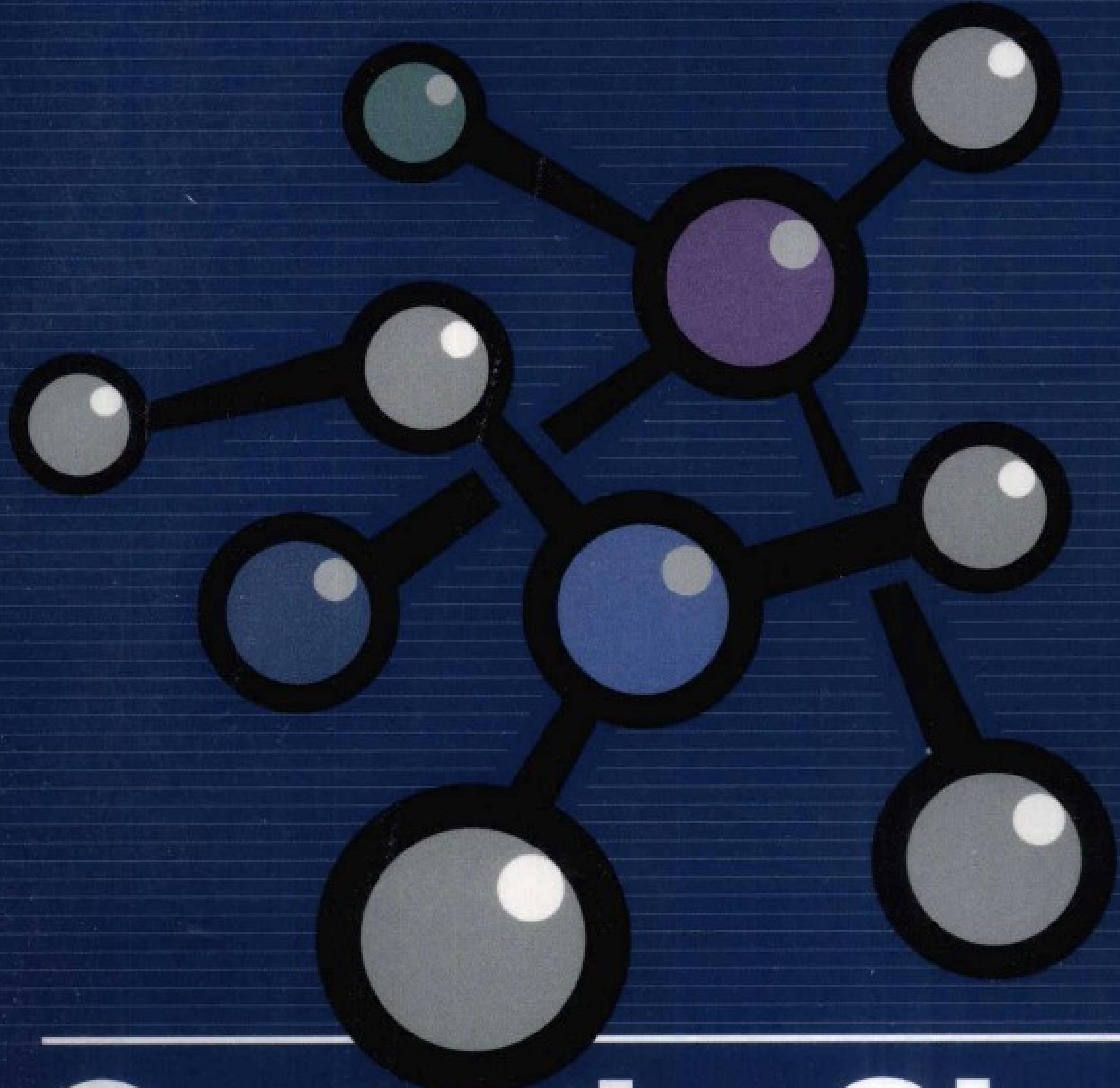

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有机化学双语教材

改编版

Sixth Edition

Organic Chemistry

有机化学

L.G. Wade, Jr. 原著
王 梅 姜文凤 改编

（第6版）

高等教育出版社
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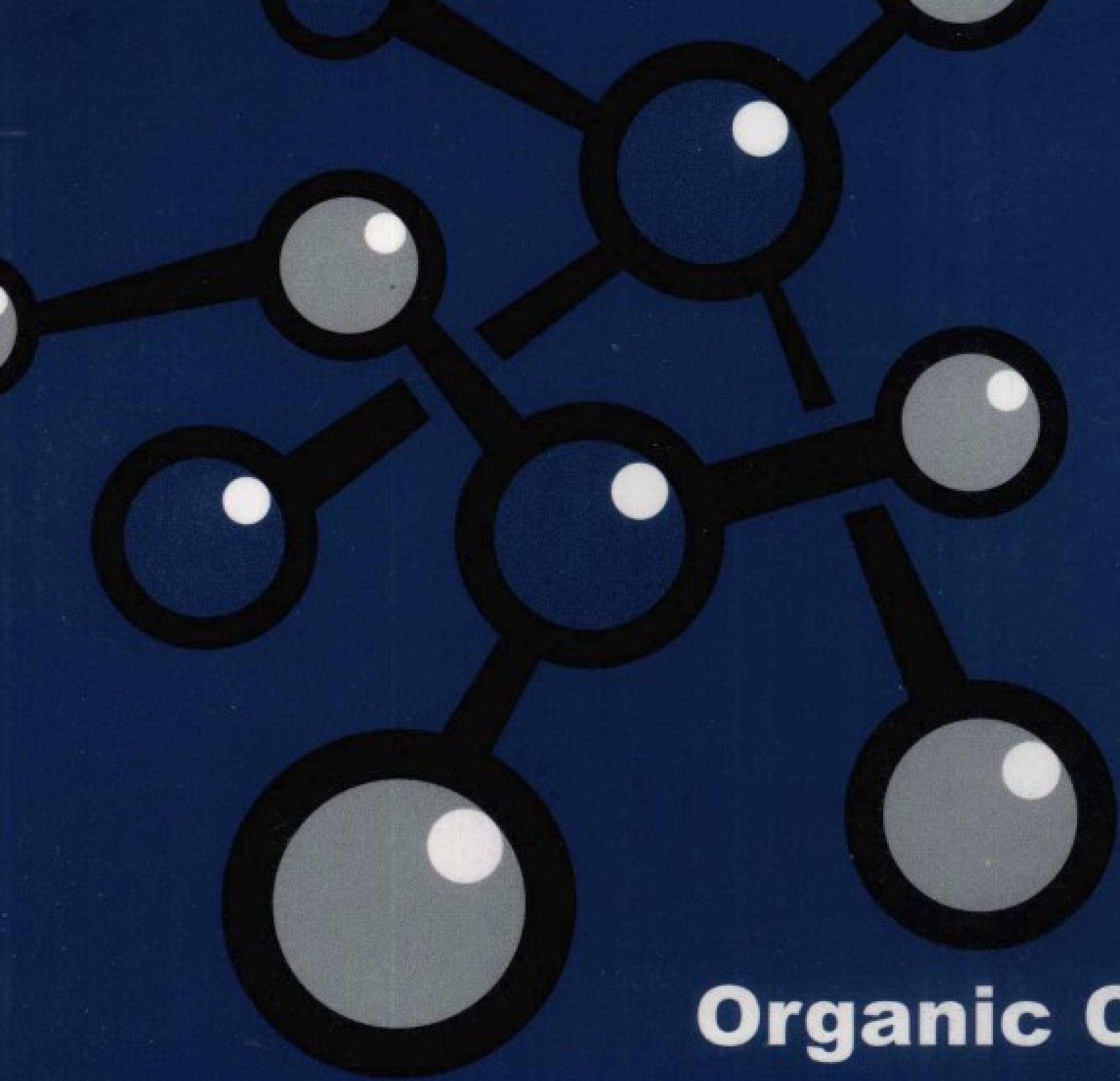

Organic Chemistry

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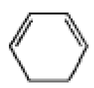
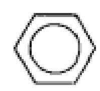
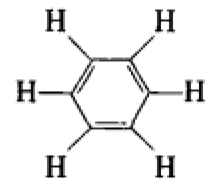
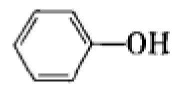
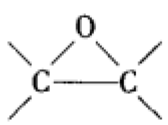
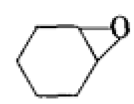
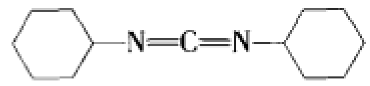
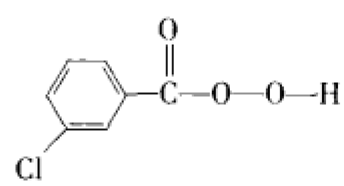
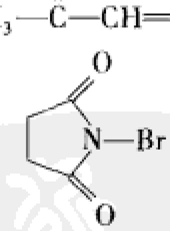
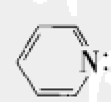
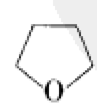
Common Organic Compounds and Functional Groups

Class of Compound	General Structure	Functional Group	Example
alkanes	$R-H$	none	$CH_3CH_2CH_2CH_3$ butane
alkyl halides	$R-X$	X = F, Cl, Br, or I	$CH_3CH_2CH_2Cl$ 1-chloropropane
alkenes	$R-CH=CH-R'$	carbon-carbon double bond	$CH_3CH_2-CH=CH_2$ 1-butene
alkynes	$R-C\equiv C-R'$	carbon-carbon triple bond	$CH_3-C\equiv C-CH_3$ 2-butyne
aromatic compounds		benzene ring, also drawn 	 benzene
alcohols	$R-OH$	hydroxyl group	CH_3CH_2-OH ethanol
phenols	$Ar-OH$	hydroxyl group on an aromatic ring	 phenol
thiols	$R-SH$	sulfhydryl group	CH_3-SH methanethiol
ethers	$R-O-R'$	oxygen between two alkyl groups	$CH_3CH_2-O-CH_2CH_3$ diethyl ether
epoxides		ether in a 3-membered ring	 1,2-epoxycyclohexane
ketones	$R-C(=O)-R'$	carbonyl group	$CH_3-C(=O)-CH_3$ acetone
aldehydes	$R-C(=O)-H$	carbonyl group	$CH_3CH_2-C(=O)-H$ propanal
carboxylic acids	$R-C(=O)-OH$	carboxyl group	$CH_3-C(=O)-OH$ acetic acid
esters	$R-C(=O)-O-R'$	carboalkoxy group	$CH_3-C(=O)-O-CH_2CH_3$ ethyl acetate
amides	$R-C(=O)-NH_2$	carboxamide group	$H-C(=O)-N(CH_3)_2$ *N*,*N*-dimethylformamide
amines	$R-NH_2$	amino group	$CH_3CH_2-NH_2$ ethylamine
nitriles	$R-C\equiv N$	cyano group	$CH_3CH_2-C\equiv N$ propionitrile
nitroalkanes	$R-NO_2$	nitro group	$CH_3CH_2-NO_2$ nitroethane

Common Reagents and Solvents

Abbreviation		Structure
Ac_2O	acetic anhydride	$CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$
DCC	dicyclohexylcarbodiimide	
DIBAL or DIBAH	diisobutylalumium hydride	$[(CH_3)_2CHCH_2]_2AlH$
DME, "glyme"	1,2-dimethoxyethane	$CH_3-O-CH_2CH_2-O-CH_3$
diglyme	bis (2-methoxyethyl) ether	$(CH_3-O-CH_2CH_2)_2O$
DMF	dimethylformamide	$H-\overset{O}{\overset{\|}{C}}-N(CH_3)_2$
DMSO	dimethyl sulfoxide	$CH_3-\overset{O}{\overset{\|}{S}}-CH_3$
EtOH	ethanol	CH_3CH_2OH
EtO^-	ethoxide ion	$CH_3CH_2-O^-$
Et_2O	diethyl ether	$CH_3CH_2-O-CH_2CH_3$
HMPA, HMPT	hexamethylphosphoric triamide	$[(CH_3)_2N]_3P=O$
LAH	lithium aluminum hydride	$LiAlH_4$
LDA	lithium diisopropylamide	$[(CH_3)_2CH]_2N^-\ Li^+$
MCPBA	*meta*-chloroperoxybenzoic acid	
MeOH	methanol	CH_3OH
MeO^-	methoxide ion	CH_3-O^-
MVK	methyl vinyl ketone	$CH_3-\overset{O}{\overset{\|}{C}}-CH=CH_2$
NBS	*N*-bromosuccinimide	
PCC	pyridinium chlorochromate	$pyr \cdot CrO_3 \cdot HCl$
Pyr	pyridine	
t-BuOH	*tertiary* butyl alcohol	$(CH_3)_3C-OH$
t-BuOK	potassium *tertiary*-butoxide	$(CH_3)_3C-O^-\ K^+$
THF	tetrahydrofuran	
TMS	tetramethylsilane	$(CH_3)_4Si$

内容提要

本书是 L. G. Wade 编写的 *Organic Chemistry*（Sixth Edition）的改编版，是根据教育部关于高等学校本科教学质量工程要重视双语教学的文件精神，选择国外优秀英文原版有机化学教材，结合双语教学的实践经验改编而成的双语教材。全书共 26 章，涵盖内容与国内高等学校化学、化工类有机化学教材基本一致，包括有机化学概论、有机化合物命名、立体化学、结构表征、烃及卤代烃、含氧化合物、含氮化合物、天然有机化合物等内容。每章后有中文概要，书后附有索引和专业词汇中英文对照表。

本书可作为化学、化工专业的有机化学双语教材，亦可作为其他相关专业的教学参考书，可使学生在学习有机化学基础知识的同时提高专业英语水平。

当删减合并；根据每章的教学重点，筛选保留部分习题；对核酸、蛋白质、甾族化合物的内容适当缩减；删掉了原版教材第26章“Synthetic Polymers”。本书涵盖内容与国内的有机化学教材内容基本一致。

7. 本书保留英文原版教材Index的部分内容，方便读者查找相关内容。

全书共26章，第1～15章由王梅改编，第16～26章由姜文凤改编；王梅通读、修改全书稿；全国高等学校首届教学名师高占先教授审查了本书的改编大纲，提出许多指导性意见；试用本书的化工英语强化班的学生提出许多宝贵意见；高等教育出版社陈琪琳和翟怡为本书出版做了许多工作；在此一并表示衷心的感谢。

本书为作者第一次将英文原版教材改编为有机化学双语教材。由于初次尝试，加之改编者水平有限，难免有不妥之处，由衷地欢迎原书作者、专家、同行和使用本书的学生提出宝贵意见，以便改进和完善这本有机化学双语教材。与本书配套的双语多媒体教学课件将随后出版，方便高等学校师生教学使用。

改编者

2008年春于大连理工大学

Preface

To the Student

As you begin your study of organic chemistry, you might feel overwhelmed by the number of compounds, names, reactions, and mechanisms that confront you. You might even wonder whether you can learn all this material in a single year. The most important function of a textbook is to organize the material to show that most of organic chemistry consists of a few basic principles and many extensions and applications of these principles. Relatively little memorization is required if you grasp the major concepts and develop flexibility in applying those concepts. Frankly, I have a poor memory, and I hate memorizing lists of information. I don't remember the specifics of most of the reactions and mechanisms in this book, but I can work them out by remembering a few basic principles, such as "alcohol dehydrations usually go by E1 mechanisms."

Still, you'll have to learn some facts and fundamental principles to serve as the working "vocabulary" of each chapter. As a student, I learned this the hard way when I made a D on my second organic chemistry exam. I thought organic would be like general chemistry, where I could memorize a couple of equations and fake my way through the exams. For example, in the ideal gas chapter, I would memorize $pV = nRT$, and I was good to go. When I tried the same approach in organic, I got a D. We learn by making mistakes, and I learned a lot in organic chemistry.

In writing this book, I've tried to point out a small number of important facts and principles that should be learned to prepare for solving problems. For example, of the hundreds of reaction mechanisms shown in this book, about 20 are the fundamental mechanistic steps that combine into the longer, more complicated mechanisms. I've highlighted these fundamental mechanisms in *Key Mechanism* boxes to alert you to their importance. Spectroscopy is another area where a student might feel pressured to memorize hundreds of facts, such as NMR chemical shifts and infrared vibration frequencies. I couldn't do that, so I've always gotten by with knowing about a dozen NMR chemical shifts and about a dozen IR vibration frequencies, and knowing how they are affected by other influences.

Don't try to memorize your way through this course. It doesn't work; you have to know what's going on so you can apply the material. Also, don't think (like I did) that you can get by without memorizing *anything*. Read the chapter, listen carefully to the lectures, and *work the problems*. The problems will tell you whether or not you know the material. If you can do the problems, you should do well on the exams. If you can't do the problems, you probably won't be able to do the exams, either. If you keep having to look up an item to do the problems, that item is a good one to learn.

Here are some hints I give my students at the beginning of the course:

1. Read the material in the book before the lecture (expect 13-15 pages per lecture). Knowing what to expect and what is in the book, you can take fewer

About the Author

L. G. Wade decided to become a chemistry major during his sophomore year at Rice University, while taking organic chemistry from Professor Ronald M. Magid. After receiving his B. A. from Rice in 1969, Wade went on to Harvard University, where he did research with Professor James D. White. While at Harvard, he served as the Head Teaching Fellow for the organic laboratories and was strongly influenced by the teaching methods of two master educators, Professors Leonard K. Nash and Frank H. Westheimer.

After completing his Ph. D. at Harvard in 1974, Dr. Wade joined the chemistry faculty at Colorado State University. Over the course of fifteen years at Colorado State, Dr. Wade taught organic chemistry to thousands of students working toward careers in all areas of biology, chemistry, human medicine, veterinary medicine, and environmental studies. He also authored research papers in organic synthesis and in chemical education, as well as eleven books reviewing current research in organic synthesis. Since 1989, Dr. Wade has been a chemistry professor at Whitman College, where he teaches organic chemistry and pursues research interests in organic synthesis and forensic chemistry. Dr. Wade received the A. E. Lange Award for Distinguished Science Teaching at Whitman in 1993.

Dr. Wade's interest in forensic science has led him to testify as an expert witness in court cases involving drugs and firearms, and he has worked as a police firearms instructor, drug consultant, and boating safety officer. He also enjoys repairing and restoring old violins and bows, which he has done professionally for many years.

CONTENTS

Chapter 1
Introduction and Review

1-1 The Origins of Organic Chemistry

The modern definition of organic chemistry is *the chemistry of carbon compounds.* What is so special about carbon that a whole branch of chemistry is devoted to its compounds? Unlike most other elements, carbon forms strong bonds to other carbon atoms and to a wide variety of other elements. Chains and rings of carbon atoms can be built up to form an endless variety of molecules. It is this diversity of carbon compounds that provides the basis for life on Earth. Living creatures are composed largely of complex organic compounds that serve structural, chemical, or genetic functions.

The term **organic** literally means "derived from living organisms." Originally, the science of organic chemistry was the study of compounds extracted from living organisms and their natural products. Compounds such as sugar, urea, starch, waxes, and plant oils were considered "organic," and people accepted **Vitalism**, the belief that natural products needed a "vital force" to create them. Organic chemistry, then, was the study of compounds having the vital force. Inorganic chemistry was the study of gases, rocks, and minerals, and the compounds that could be made from them.

In the nineteenth century, experiments showed that organic compounds could be synthesized from inorganic compounds. In 1828, the German chemist Friedrich Wöhler converted ammonium cyanate, made from ammonia and cyanic acid, to urea simply by heating it in the absence of oxygen.

$$NH_4^+ \ {}^-OCN \xrightarrow{\text{heat}} H_2N\text{—}\overset{\overset{\Large O}{\|}}{C}\text{—}NH_2$$

ammonium cyanate (氰酸铵) (inorganic) → urea (尿素) (organic)

Urea had always come from living organisms and was presumed to contain the vital force, yet ammonium cyanate is inorganic and thus lacks the vital force. Some chemists claimed that a trace of vital force from Wöhler's hands must have contaminated the reaction, but most recognized the possibility of synthesizing organic compounds from inorganics. Many other syntheses were carried out, and the vital force theory was eventually discarded.

Even though organic compounds do not need a vital force, they are still distinguished from inorganic compounds. The distinctive feature of organic compounds is that they *all* contain one or more carbon atoms. Still, not all carbon compounds are organic; substances such as diamond, graphite, carbon dio-xide, ammonium cyanate, and sodium carbonate are derived from minerals and have typical inorganic properties. Most of the millions of carbon compounds are classified as organic, however.

We ourselves are composed largely of organic molecules, and we are nourished by the organic compounds in our food. The proteins in our skin, the lipids in our cell membranes, the glycogen in our livers, and the DNA in the nuclei of our cells are all organic compounds. Our bodies are also regulated and defended by complex organic compounds.

Chemists have learned to synthesize or simulate many of these complex molecules. The synthetic products serve as drugs, medicines, plastics, pesticides, paints, and fibers. Many of the most important advances in medicine are actually advances in organic chemistry. New synthetic drugs are developed to combat disease, and new polymers are molded to replace failing organs. Organic chemistry has gone full circle. It began as the study of compounds derived from "organs," and now it gives us the drugs and materials we need to save or replace those organs.

1-2 Principles of Atomic Structure

Before we begin our study of organic chemistry, we must review some basic principles. Many of these concepts of atomic and molecular structure are crucial to your understanding of the structure and bonding of organic compounds.

1-2A Structure of the Atom

Atoms are made up of protons, neutrons, and electrons. Protons are positively charged and are found together with (uncharged) neutrons in the nucleus. Electrons, which have a negative charge that is equal in magnitude to the positive charge on the proton, occupy the space surrounding the nucleus (Figure 1-1). Protons and neutrons have similar masses, about 1 800 times the mass of an electron. Almost all the atom's mass is in the nucleus, but it is the electrons that take part in chemical bonding and reactions.

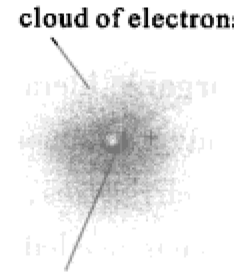


Figure 1-1 Basic atomic structure. An atom has a dense, positively charged nucleus surrounded by a cloud of electrons.

Each element is distinguished by the number of protons in the nucleus (the atomic number). The number of neutrons is usually similar to the number of protons, although the number of neutrons may vary. Atoms with the same number of protons but different numbers of neutrons are called **isotopes**. For example, the most common kind of carbon atom has six protons and six neutrons in its nucleus. Its mass number (the sum of the protons and neutrons) is 12, and we write its symbol as ^{12}C. About 1% of carbon atoms have seven neutrons; the mass number is 13, written ^{13}C. A very small fraction of carbon atoms have eight neutrons and a mass number of 14. The ^{14}C isotope is radioactive, with a half-life (the time it takes for half of the nuclei to decay) of 5 730 years. The predictable decay of ^{14}C is used to determine the age of organic materials up to about 50 000 years old.

1-2B Electronic Structure of the Atom

An element's chemical properties are determined by the number of protons in the nucleus and the corresponding number of electrons around the nucleus. The electrons form bonds and determine the structure of the resulting molecules. Because they are small and light, electrons show properties of both particles and waves; in many ways, the electrons in atoms and molecules behave more like waves than like particles.

Electrons that are bound to nuclei are found in **orbitals**. The *Heisenberg uncertainty principle* states that we

can never determine exactly where the electron is; nevertheless, we can determine the **electron density**, the probability of finding the electron in a particular part of the orbital. An orbital, then, is an allowed energy state for an electron, with an associated probability function that defines the distribution of electron density in space.

Atomic orbitals are grouped into different "shells" at different distances from the nucleus. Each shell is identified by a principal quantum number n, with $n = 1$ for the lowest-energy shell closest to the nucleus. As n increases, the shells are farther from the nucleus, higher in energy, and can hold more electrons. Most of the common elements in organic compounds are found in the first two rows of the periodic table, indicating that their electrons are found in the first two electron shells. The first shell($n = 1$) can hold two electrons, and the second shell($n = 2$) can hold eight.

The first electron shell contains just the 1*s* orbital. All *s* orbitals are spherically symmetrical, meaning that they are nondirectional. The electron density is only a function of the distance from the nucleus. The electron density of the 1*s* orbital is graphed in Figure 1-2. Notice how the electron density is highest *at* the nucleus and falls off exponentially with increasing distance from the nucleus.

The second electron shell consists of the 2*s* and 2*p* orbitals. The 2*s* orbital is spherically symmetrical like the 1*s* orbital, but its electron density is not a simple exponential function. The 2*s* orbital has a smaller amount of electron density close to the nucleus.

Most of the electron density is farther away, beyond a region of zero electron density called a **node**. Because most of the 2*s* electron density is farther from the nucleus than that of the 1*s*, the 2*s* orbital is higher in energy. Figure 1-3 shows a graph of the 2*s* orbital.

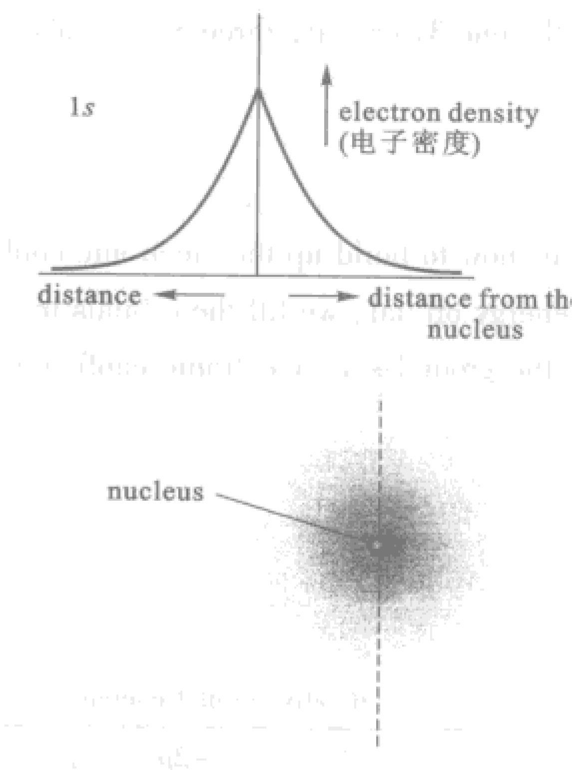


Figure 1-2 Graph and diagram of the 1*s* atomic orbital.

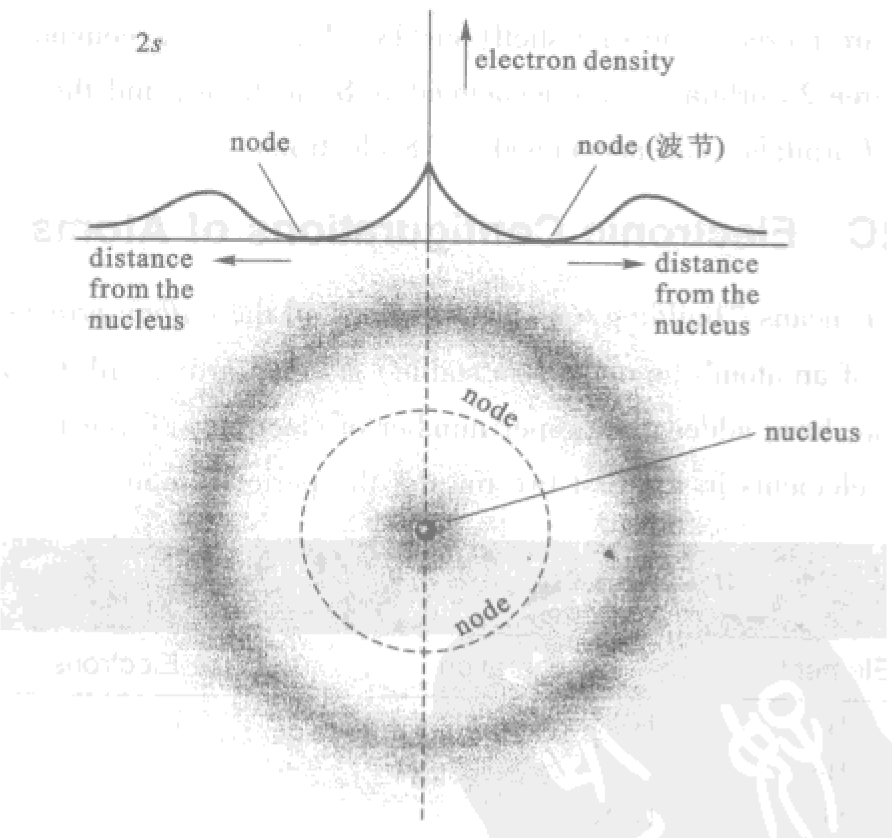


Figure 1-3 Graph and diagram of the 2*s* atomic orbital.

In addition to the 2*s* orbital, the second shell also contains three 2*p* atomic orbitals, one oriented in each of the three spatial directions. These orbitals are called the $2p_x$, the $2p_y$, and the $2p_z$, according to their direction along the x, y, or z axis. The 2*p* orbitals are slightly higher in energy than the 2*s*, because the average location of the electron in a 2*p* orbital is farther from the nucleus. Each *p* orbital consists of two lobes, one on either side of the nucleus, with a **nodal plane** at the nucleus. The nodal plane is a flat(planar) region of space, including the

nucleus, with zero electron density. The three $2p$ orbitals differ only in their spatial orientation, so they have identical energies. Orbitals with identical energies are called **degenerate orbitals**. Figure 1−4 shows the shapes of the three degenerate $2p$ atomic orbitals.

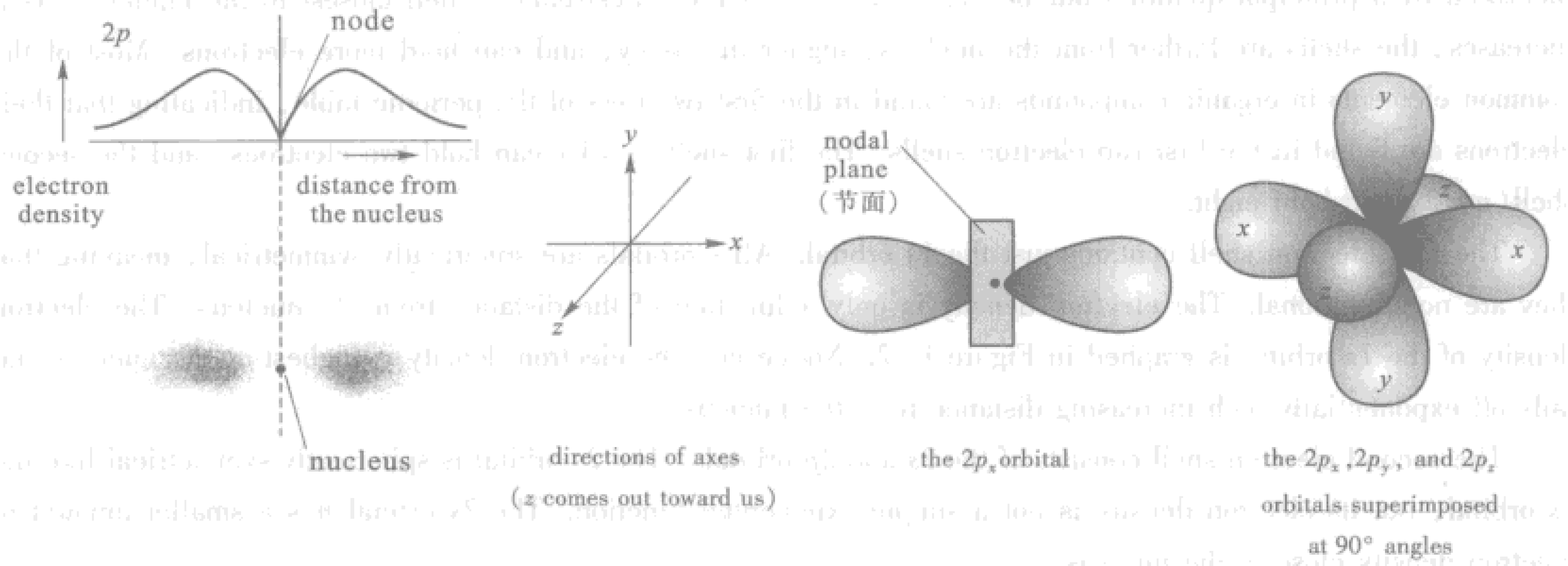


Figure 1−4 The $2p$ orbitals. There are three $2p$ orbitals, oriented at right angles to each other. Each is labeled according to its orientation along the x, y or z axis.

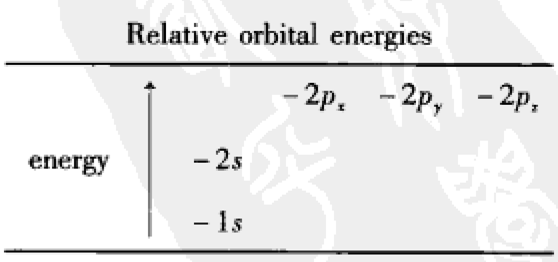
The *Pauli exclusion principle* tells us that each orbital can hold a maximum of 2 electrons, provided that their spins are paired. The first shell (one $1s$ orbital) can accommodate 2 electrons. The second shell (one $2s$ orbital and three $2p$ orbitals) can accommodate 8 electrons, and the third shell (one $3s$ orbital, three $3p$ orbitals, and five $3d$ orbitals) can accommodate 18 electrons.

1−2C Electronic Configurations of Atoms

Aufbau means "building up" in German, and the *aufbau principle* tells us how to build up the electronic configuration of an atom's ground (most stable) state. Starting with the lowest-energy orbital, we fill the orbitals in order until we have added the proper number of electrons. Table 1−1 shows the ground-state electronic configurations of the elements in the first two rows of the periodic table.

TABLE 1−1 Electronic Configurations of the Elements of the First and Second Rows

Element	Configuration	Valence Electrons
H	$1s^1$	1
He	$1s^2$	2
Li	$1s^2 2s^1$	1
Be	$1s^2 2s^2$	2
B	$1s^2 2s^2 2p_x^1$	3
C	$1s^2 2s^2 2p_x^1 2p_y^1$	4
N	$1s^2 2s^2 2p_x^1 2p_y^1 2p_z^1$	5
O	$1s^2 2s^2 2p_x^2 2p_y^1 2p_z^1$	6
F	$1s^2 2s^2 2p_x^2 2p_y^2 2p_z^1$	7
Ne	$1s^2 2s^2 2p_x^2 2p_y^2 2p_z^2$	8



Two additional concepts are illustrated in Table 1−1. The **valence electrons** are those electrons that are in

the outermost shell. Carbon has four valence electrons, nitrogen has five, and oxygen has six. Helium has two valence electrons and neon has eight, corresponding to a filled first shell and second shell, respectively. In general (for the representative elements), the column or group number of the periodic table corresponds to the number of valence electrons. Hydrogen and lithium have one valence electron, and they are both in the first column (group IA) of the periodic table. Carbon has four valence electrons, and it is in group IVA of the periodic table.

Notice in Table 1–1 that carbon's third and fourth valence electrons are not paired; they occupy separate orbitals. Although the Pauli exclusion principle says that two electrons can occupy the same orbital, the electrons repel each other, and pairing requires additional energy. **Hund's rule** states that when there are two or more orbitals of the same energy, electrons will go into *different* orbitals rather than pair up in the same orbital. The first $2p$ electron (boron) goes into one $2p$ orbital, the second (carbon) goes into a different orbital, and the third (nitrogen) occupies the last $2p$ orbital. The fourth, fifth, and sixth $2p$ electrons must pair up with the first three electrons.

PROBLEM 1–1

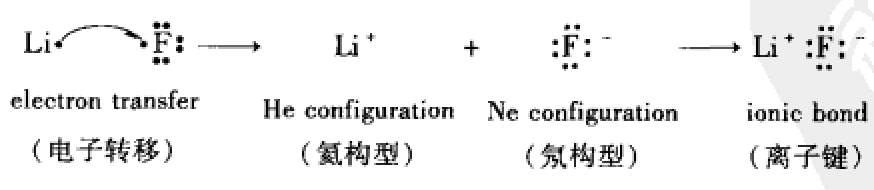
Write the electronic configurations of the third-row elements shown in the first three rows of the periodic table.

1–3 Bond Formation: The Octet Rule

In 1915, G. N. Lewis proposed several new theories describing how atoms bond together to form molecules. One of these theories states that a filled shell of electrons is especially stable, and *atoms transfer or share electrons in such a way as to attain a filled shell of electrons.* A filled shell of electrons is simply the electron configuration of a noble gas, such as He, Ne, or Ar. This principle has come to be called the **octet rule** because a filled shell implies eight valence electrons for the elements in the second row of the periodic table.

1–3A Ionic Bonding

There are two ways that atoms can interact to attain noble-gas configurations. Sometimes atoms attain noble-gas configurations by transferring electrons from one atom to another. For example, lithium has one electron more than the helium configuration, and fluorine has one electron less than the neon configuration. Lithium easily loses its valence electron, and fluorine easily gains one:



A transfer of one electron gives each of these two elements a noble-gas configuration. The resulting ions have opposite charges, and they attract each other to form an **ionic bond**. Ionic bonding usually results in the formation of a large crystal lattice rather than individual molecules. Ionic bonding is common in inorganic compounds but relatively uncommon in organic compounds.

1–3B Covalent Bonding

Covalent bonding, in which electrons are shared rather than transferred, is the most common type of bonding in

organic compounds. Hydrogen, for example, needs a second electron to achieve the noble-gas configuration of helium. If two hydrogen atoms come together and form a bond, they "share" their two electrons, and each atom has two electrons in its valence shell.

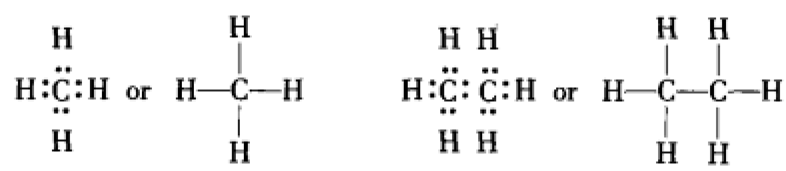
$$H\cdot + H\cdot \longrightarrow H:H$$ each H shares two electrons (He configuration)

We will study covalent bonding in more detail in Chapter 2.

1-4 Lewis Structures

One way to symbolize the bonding in a covalent molecule is to use **Lewis structures**. In a Lewis structure, each valence electron is symbolized by a dot. A bonding pair of electrons is symbolized by a pair of dots or by a dash (—). We try to arrange all the atoms so they have their appropriate noble-gas configurations: two electrons for hydrogen, and octets for the second-row elements.

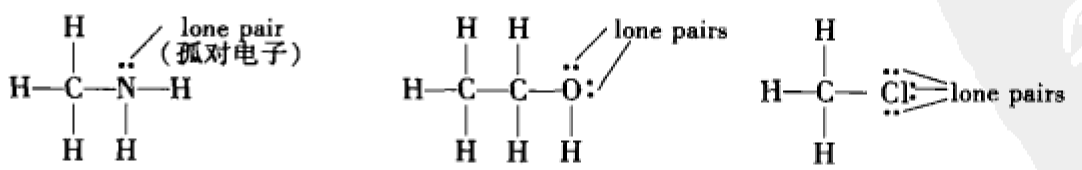
Consider the Lewis structure of methane (CH_4). Carbon contributes four valence electrons, and each hydrogen contributes one, to give a total of eight electrons. All eight electrons surround carbon to give it an octet, and each hydrogen atom shares two of the electrons.



methane (甲烷) ethane (乙烷)

The Lewis structure for ethane (C_2H_6) is more complex. Once again, we have computed the total number of valence electrons (14) and distributed them so that each carbon atom is surrounded by 8 and each hydrogen by 2. The only possible structure for ethane is the one shown, with the two carbon atoms sharing a pair of electrons and each hydrogen atom sharing a pair with one of the carbons. The ethane structure shows the most important characteristic of carbon—its ability to form strong carbon-carbon bonds.

Valence-shell electrons that are *not* shared between two atoms are called **nonbonding electrons**. A pair of nonbonding electrons is often called a **lone pair**. Oxygen atoms, nitrogen atoms, and the halogens (F, Cl, Br, I) usually have nonbonding electrons in their stable compounds. These lone pairs of nonbonding electrons help to determine the reactivity of their parent compounds. The following Lewis structures show one lone pair of electrons on the nitrogen atom of methylamine and two lone pairs on the oxygen atom of ethanol. Halogen atoms usually have three lone pairs, as shown in the structure of chloromet-hane.



methylamine (甲胺) ethanol (乙醇) chloromethane (氯代甲烷)

A correct Lewis structure should show any lone pairs. Organic chemists often draw structures that omit most or all of the lone pairs. These are not true Lewis structures because you must imagine the correct number of nonbonding electrons.

PROBLEM 1-2

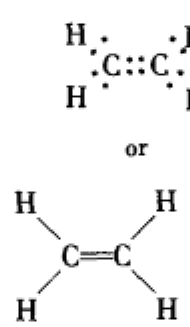
Draw Lewis structures for the following compounds.

(a) ammonia, NH_3(氨)
(b) water, H_2O
(c) hydronium ion, H_3O^+(水合氢离子)
(d) propane, C_3H_8(丙烷)
(e) ethylamine, $CH_3CH_2NH_2$(乙胺)
(f) dimethyl ether, CH_3OCH_3(二甲醚)
(g) fluoroethane, CH_3CH_2F(氟代乙烷)
(h) 2-propanol, $CH_3CH(OH)CH_3$(2-丙醇)
(i) borane, BH_3(硼烷)
(j) boron trifluoride, BF_3(三氟化硼)

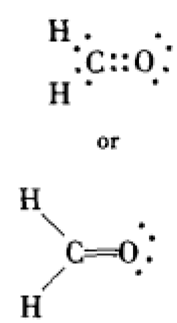
Explain what is unusual about the bonding in compounds in parts (i) and (j).

1-5 Multiple Bonding

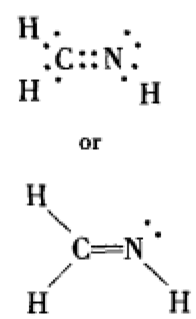
In drawing Lewis structures in Section 1-4, we placed just one pair of electrons between any two atoms. The sharing of one pair between two atoms is called a **single bond**. Many molecules have adjacent atoms sharing two or even three electron pairs. The sharing of two pairs is called a **double bond**, and the sharing of three pairs is called a **triple bond**. Ethylene (C_2H_4) is an organic compound with a double bond. When we draw a Lewis structure for ethylene, the only way to show both carbon atoms with octets is to draw them sharing two pairs of electrons. The following examples show organic compounds with double bonds. In each case, four electrons (two pairs) are shared between two atoms to give them octets. A double dash (=) symbolizes a double bond.



ethylene
(乙烯)

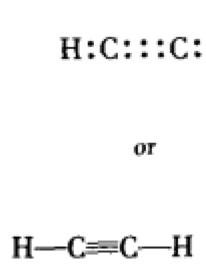


formaldehyde
(甲醛)

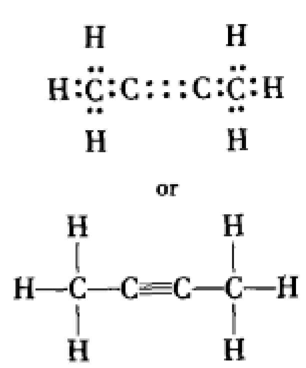


formaldimine
(甲醛亚胺,甲亚胺)

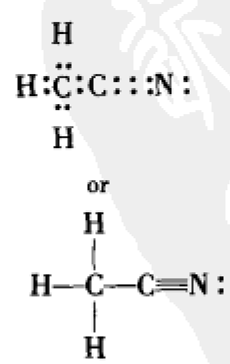
Acetylene (C_2H_2) has a triple bond. Its Lewis structure shows three pairs of electrons between the carbon atoms to give them octets. The following examples show organic compounds with triple bonds. A triple dash (≡) symbolizes a triple bond.



acetylene
(乙炔)



dimethylacetylene
(二甲基乙炔)

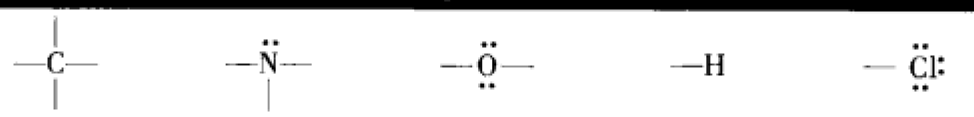


acetonitrile
(乙腈)

All these Lewis structures show that carbon normally forms four bonds in neutral organic compounds. Nitrogen generally forms three bonds, and oxygen usually forms two. Hydrogen and the halogens usually form only one

bond. The number of bonds an atom usually forms is called its **valence**. Carbon is tetravalent, nitrogen is trivalent, oxygen is divalent, and hydrogen and the halogens are monovalent. By remembering the usual number of bonds for these common elements, we can write organic structures more easily. If we draw a structure with each atom having its usual number of bonds, a correct Lewis structure usually results.

SUMMARY Common Bonding Patterns (Uncharged)



	carbon	nitrogen	oxygen	hydrogen	halogens
valence:	4	3	2	1	1
lone pairs:	0	1	2	0	3

PROBLEM 1-3

Write Lewis structures for the following molecular formulas.

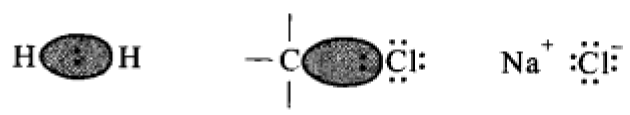
(a) N_2 (b) HCN (c) HONO
(d) CO_2 (e) H_2CNH (f) HCO_2H
(g) C_2H_3Cl (h) HNNH (i) C_3H_6
(j) C_3H_4 (two double bonds) (k) C_3H_4 (one triple bond)

PROBLEM 1-4

Circle any lone pairs (pairs of nonbonding electrons) in the structures you drew for Problem 1-3.

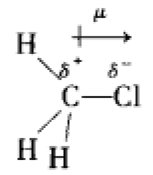
1-6 Electronegativity and Bond Polarity

A bond with the electrons shared equally between the two atoms is called a **nonpolar covalent bond**. The bond in H_2 and the C—C bond in ethane are nonpolar covalent bonds. In most bonds between two different elements, the bonding electrons are attracted more strongly to one of the two nuclei. An unequally shared pair of bonding electrons is called a **polar covalent bond**.



nonpolar (非极性) covalent bond (共价键) polar (极性) covalent bond ionic bond (离子键)

When carbon is bonded to chlorine, for example, the bonding electrons are attracted more strongly to the chlorine atom. The carbon atom bears a small partial positive charge, and the chlorine atom bears an equal amount of negative charge. Figure 1-5 shows the polar carbon-chlorine bond in chloromethane. We symbolize the bond polarity by an arrow with its head at the negative end of the polar bond and a plus sign at the positive end. The bond polarity is measured by its **dipole moment** (μ), defined to be the amount of charge separation (δ^+ and δ^-) multiplied by the bond length. The symbol δ^+ means "a small amount of positive charge"; δ^- means "a small amount of negative charge".



chloromethane

Figure 1–5 Bond polarity. Chloromethane contains a polar carbon-chlorine bond with a partial negative charge on chlorine and a partial positive charge on carbon.

H 2.2						
Li 1.0	Be 1.6	B 1.8	C 2.5	N 3.0	O 3.4	F 4.0
Na 0.9	Mg 1.3	Al 1.6	Si 1.9	P 2.2	S 2.6	Cl 3.2
K 0.8						Br 3.0
						I 2.7

Figure 1–6 The Pauling electronegativities of some of the elements found in organic compounds.

We often use **electronegativities** as a guide in predicting whether a given bond will be polar and the direction of its dipole moment. The Pauling electronegativity scale, most commonly used by organic chemists, is based on bonding properties, and it is useful for predicting the polarity of covalent bonds. Elements with higher electronegativities generally have more attraction for the bonding electrons. Therefore, in a bond between two different atoms, the atom with the higher electronegativity is the negative end of the dipole. Figure 1–6 shows Pauling electronegativities for some of the important elements in organic compounds.

Notice that the electronegativities increase from left to right across the periodic table. Nitrogen, oxygen, and the halogens are all more electronegative than carbon; sodium, lithium, and magnesium are less electronegative. Hydrogen's electronegativity is similar to that of carbon, so we usually consider C—H bond to be nonpolar. We will consider the polarity of bonds and molecules in more detail in Section 2–9.

PROBLEM 1–5

Use electronegativities to predict the direction of the dipole moments of the following bonds.

(a) C—Cl **(b)** C—O **(c)** C—N **(d)** C—S **(e)** C—B
(f) N—Cl **(g)** N—O **(h)** N—S **(i)** N—B **(j)** B—Cl

1–7 Formal Charges

In polar bonds, the partial charges (δ^+ and δ^-) on the bonded atoms are *real.* **Formal charges** provide a method for keeping track of electrons, but they may or may not correspond to real charges. In most cases, if the Lewis structure shows that an atom has a formal charge, it actually bears at least part of that charge. The concept of formal charge helps us determine which atoms bear most of the charge in a charged molecule, and it also helps us to see charged atoms in molecules that are neutral overall.

To calculate formal charges, count how many electrons contribute to the charge of each atom and compare that number with the number of valence electrons in the free, neutral atom (given by the group number in the periodic table). The electrons that contribute to an atom's charge are:

1. *all* its unshared (nonbonding) electrons;

2. *half* the (bonding) electrons it shares with other atoms, or one electron of each bonding pair.

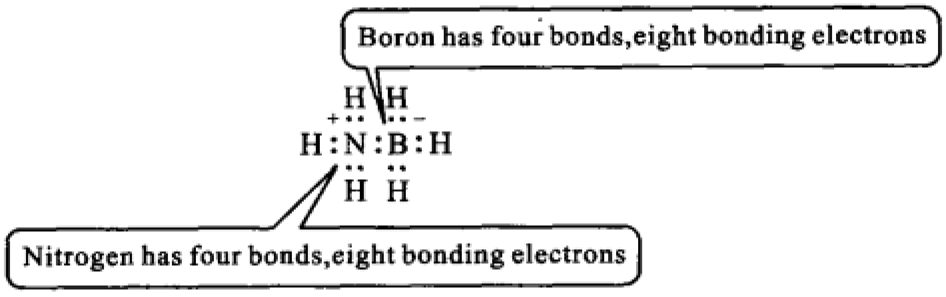
The formal charge of a given atom can be calculated by the formula

$$\text{formal charge (FC)} = [\text{group number}] - [\text{nonbonding electrons}] - \frac{1}{2}[\text{shared electrons}]$$

SOLVED PROBLEM 1-1

Compute the formal charge (FC) on each atom in the following structures.

(a) $H_3\overset{+}{N}—\overset{-}{B}H_3$



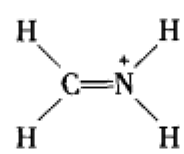
SOLUTION

This is a neutral compound where the individual atoms are formally charged. The Lewis structure shows that both nitrogen and boron have four shared bonding pairs of electrons. Both boron and nitrogen have $\frac{8}{2} = 4$ electrons contributing to their charges. Nitrogen (group V) needs five valence electrons to be neutral, so it bears a formal charge of +1. Boron (group Ⅲ) needs only three valence electrons to be neutral, so it bears a formal charge of −1.

Nitrogen (氮): $FC = 5 - 0 - \frac{1}{2}(8) = +1$

Boron (硼): $FC = 3 - 0 - \frac{1}{2}(8) = -1$

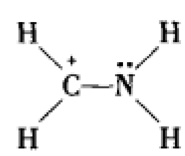
(b) $[H_2CNH_2]^+$



SOLUTION

In this structure, both carbon and nitrogen have four shared pairs of bonding electrons. With four bonds, carbon is formally neutral; however, nitrogen is in group V, and it bears a formal positive charge: $FC = 5 - 0 - 4 = +1$.

This compound might also be drawn with the following Lewis structure:



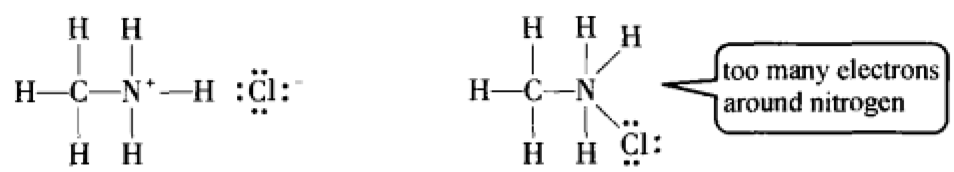
In this structure, the carbon atom has three bonds with six bonding electrons. We calculate that $\frac{6}{2} = 3$ electrons, so carbon is one short of the four needed to be formally neutral: $FC = 4 - 0 - \frac{1}{2}(6) = +1$.

Nitrogen has six bonding electrons and two nonbonding electrons. We calculate that $\frac{6}{2} + 2 = 5$, so the nitrogen is uncharged in this second structure: $FC = 5 - 2 - \frac{1}{2}(6) = 0$

The significance of these two Lewis structures is discussed in Section 1-9.

1-8 Ionic Structures

Some organic compounds contain ionic bonds. For example, the structure of methylammonium chloride (CH_3NH_3Cl) cannot be drawn using just covalent bonds. That would require nitrogen to have five bonds, implying ten electrons in its valence shell. The correct structure shows the chloride ion ionically bonded to the rest of the structure.



methylammonium chloride (甲基氯化铵)　　cannot be drawn covalently

SUMMARY Common Bonding Patterns in Organic Compounds and Ions

Atom	Valence Electrons	Positively Charged	Neutral	Negatively Charged
B	3		—B— (no octet)	—B⁻—
C	4	—C⁺— (no octet) (非八电子)	—C—	—C̈⁻—
N	5	—N⁺—	—N̈—	—N̈⁻—
O	6	—Ö⁺—	—Ö—	—Ö:⁻
halogen	7	—C̈l⁺—	—C̈l:	:C̈l:⁻

Some molecules can be drawn either covalently or ionically. For example, sodium acetate ($NaOCOCH_3$) may be drawn with either a covalent bond or an ionic bond between sodium and oxygen. Because sodium generally forms ionic bonds with oxygen (as in NaOH), the ionically bonded structure is usually preferred. In general, bonds between atoms with very large electronegativity differences (about 2 or more) are usually drawn as ionic.

PROBLEM 1-6

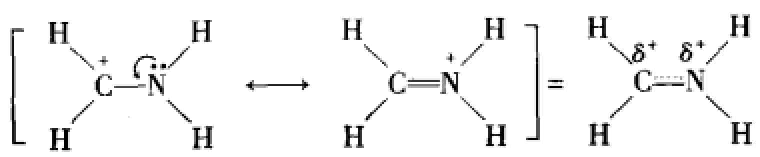
Draw Lewis structures for the following compounds and ions, showing appropriate formal charges.

(a) $[CH_3OH_2]^+$　(b) NH_4Cl　(c) $(CH_3)_2NH_2Cl$
(d) $NaOCH_3$　(e) $^+CH_3$　(f) $^-CH_3$
(g) $NaBH_4$　(h) $NaBH_3CN$　(i) $(CH_3)_2O{-}BF_3$
(j) $[HONH_3]^+$　(k) $KOC(CH_3)_3$　(l) $[H_2C{=}OH]^+$

1-9 Resonance

1-9A Resonance Hybrids

Some compounds'structures are not adequately represented by a single Lewis structure. When two or more valence-bond structures are possible, differing only in the placement of electrons, the molecule will usually show characteristics of both structures. The different structures are called **resonance structures** or **resonance forms** because they are not different compounds, just different ways of drawing the same compound. The actual molecule is said to be a **resonance hybrid** of its resonance forms. In Solved Problem 1-1(b) we saw that the ion $[H_2CNH_2]^+$ might be represented by either of the following resonance forms:



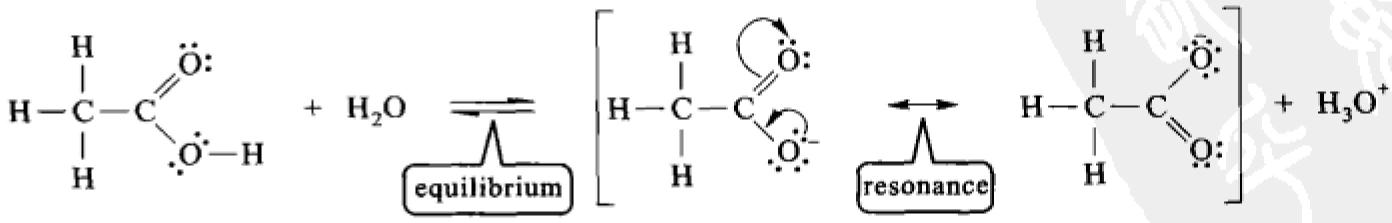
resonance forms of a resonance hybrid
(共振杂化体的共振式)

combined representation

The actual structure of this ion is a resonance hybrid of the two structures. In the actual molecule, the positive charge is **delocalized** (spread out) over both the carbon atom and the nitrogen atom. In the left resonance form, the positive charge is on carbon, but carbon does not have an octet. Nitrogen's nonbonding electrons can move into the bond to give the second structure with a double bond a positive charge on nitrogen and an octet on carbon. The combined representation attempts to combine the two resonance forms into a single picture with the charge shared by carbon and nitrogen.

Spreading the positive charge over two atoms makes the ion more stable than it would be if the entire charge were localized only on the carbon or only on the nitrogen. We call this a **resonance-stabilized** cation. Resonance is most important when it allows a charge to be delocalized over two or more atoms, as in this example.

Resonance stabilization plays a crucial role in organic chemistry, especially in the chemistry of compounds having double bonds. We will use the concept of resonance frequently throughout this course. For example, the acidity of acetic acid (following) is enhanced by resonance effects. When acetic acid loses a proton, the resulting acetate ion has a negative charge delocalized over both of the oxygen atoms. Each oxygen atom bears half of the negative charge, and this delocalization stabilizes the ion. Each of the carbon-oxygen bonds is halfway between a single bond and a double bond, and they are said to have a *bond order* of $1\frac{1}{2}$.

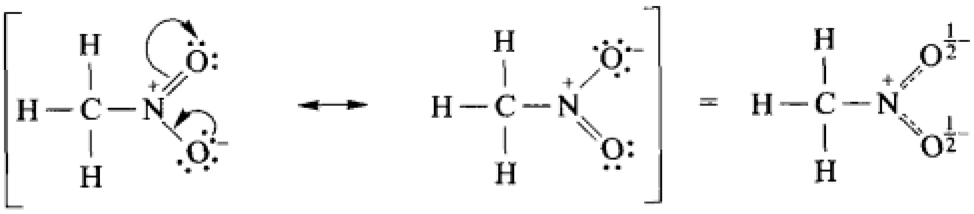


acetic acid
(乙酸,醋酸)

acetate ion
(乙酸根离子)

We use a single double-headed arrow between resonance forms (and often enclose them in brackets) to indicate that the actual structure is a hybrid of the Lewis structures we have drawn. By contrast, an equilibrium is represented by two arrows in opposite directions.

Some uncharged molecules actually have resonance-stabilized structures with equal positive and negative formal charges. We can draw two Lewis structures for nitromethane (CH_3NO_2), but both of them have a formal positive charge on nitrogen and a negative charge on one of the oxygens. Thus, nitromethane has a positive charge on the nitrogen atom and a negative charge spread equally over the two oxygen atoms. The N—O bonds are midway between single and double bonds, as indicated in the combined representation:



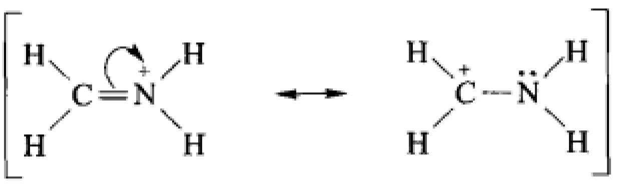
resonance forms
(共振式)

combined representation

Remember that individual resonance forms do not exist. The molecule does not "resonate" between these structures. It is a hybrid with some characteristics of both. An analogy is a mule, which is a hybrid of a horse and a donkey. The mule does not "resonate" between looking like a horse and looking like a donkey; it looks like a mule all the time, with the broad back of the horse and the long ears of the donkey.

1-9B Major and Minor Resonance Contributors

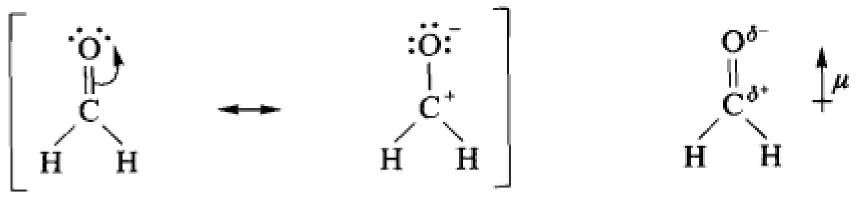
Two or more correct Lewis structures for the same compound may or may not represent electron distributions of equal energy. Although separate resonance forms do not exist, we can estimate their relative energies as if they did exist. More stable resonance forms are closer representations of the real molecule than less stable ones. The two resonance forms shown earlier for the acetate ion have similar bonding, and they are of identical energy. The same is true for the two resonance forms of nitromethane. The following resonance forms are bonded differently, however.



major contributor   minor contributor

These structures are not equal in estimated energy. The first structure has the positive charge on nitrogen. The second has the positive charge on carbon, and the carbon atom does not have an octet. The first structure is more stable because it has an additional bond and all the atoms have octets. Many stable ions have a positive charge on a nitrogen atom with four bonds. We call the more stable resonance form the **major contributor**, and the less stable form is the **minor contributor**. The structure of the actual compound resembles the major contributor more than it does the minor contributor.

Many organic molecules have major and minor resonance contributors. Formaldehyde ($H_2C{=}O$) can be written with a negative charge on oxygen, balanced by a positive charge on carbon. This polar resonance form is higher in estimated energy than the double-bonded structure because it has charge separation, fewer bonds, and a positively charged carbon atom without an octet. The charge-separated structure is only a minor contributor, but it helps to explain why the formaldehyde C=O bond is very polar, with a partial positive charge on carbon and a partial negative charge on oxygen.



all octets
no charge separation
(major contributor)

no octet on C
charge separation
(minor contributor)

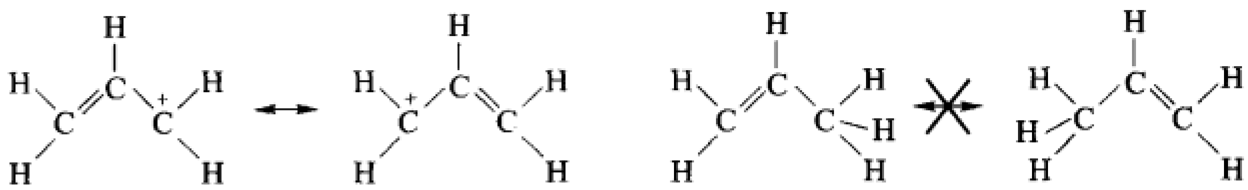
dipole moment
(偶极矩)

In drawing resonance forms, we try to draw structures that are as low in energy as possible. The best candidates are those that have the maximum number of octets and the maximum number of bonds. Also, we look for structures with the minimum amount of charge separation.

Only electrons can be delocalized. Unlike electrons, nuclei cannot be delocalized. They must remain in the same places, with the same bond distances and angles, in all the resonance contributors. The following general rules will help us to draw realistic resonance structures:

1. All the resonance structures must be valid Lewis structures for the compound.

2. Only the placement of the electrons may be shifted from one structure to another. (Electrons in double bonds and lone pairs are the ones that are most commonly shifted.) Nuclei cannot be moved, and the bond angles must remain the same.



resonance forms
(共振式)

NOT resonance

3. The number of unpaired electrons (if any) must remain the same. Most stable compounds have no unpaired electrons, and all the electrons must remain paired in all the resonance structures.

4. The major resonance contributor is the one with the lowest energy. Good contributors generally have all octets satisfied, as many bonds as possible, and as little charge separation as possible. Negative charges are more stable on more electronegative atoms, such as O, N, and S.

5. Resonance stabilization is most important when it serves to delocalize a charge over two or more atoms.

Resonance forms can be compared using the following criteria, beginning with the most important:

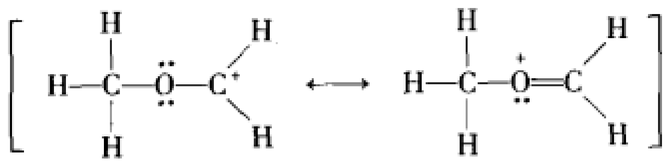
1. As many octets as possible.
2. As many bonds as possible.
3. Any negative charges on electronegative atoms.
4. As little charge separation as possible.

SOLVED PROBLEM 1-2

For each of the following compounds, draw the important resonance forms. Indicate which structures are major and minor contributors or whether they would have the same energy.

(a) $[CH_3OCH_2]^+$

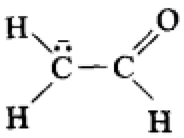
SOLUTION



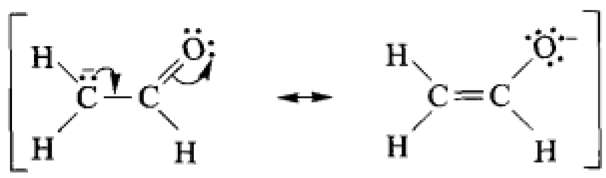
minor contributor major contributor

The first (minor) structure has a carbon atom with only six electrons around it. The second (major) structure has octets on all atoms and an additional bond.

(b)



SOLUTION



minor contributor major contributor

Both of these structures have octets on oxygen and both carbon atoms, and they have the same number of bonds. The first structure has the negative charge on carbon; the second has it on oxygen. Oxygen is the more electronegative element, so the second structure is the major contributor.

PROBLEM 1−7

Draw the important resonance forms for the following molecules and ions.

(a) CO_3^{2-} **(b)** NO_3^- **(c)** NO_2^- **(d)** $H_2C{=}CH{-}CH_2^+$

(e) $H_2C{=}CH{-}CH_2^-$ **(f)** SO_4^{2-} **(g)** $[CH_3C(OCH_3)_2]^+$

PROBLEM 1−8

For each of the following compounds, draw the important resonance forms. Indicate which structures are major and minor contributors or whether they have the same energy.

(a) $[H_2CNO_2]^-$ **(b)** $H_2C{=}CH{-}NO_2$ **(c)** $[H_2COH]^+$

(d) H_2CNN **(e)** $[H_2CCN]^-$ **(f)** $H_2N{-}\overset{+}{C}H{-}CH{=}CH{-}NH_2$

(g) $H{-}\overset{O}{\overset{\|}{C}}{-}\overset{-}{C}H{-}\overset{O}{\overset{\|}{C}}{-}H$ **(h)** $H{-}\overset{O}{\overset{\|}{C}}{-}NH_2$

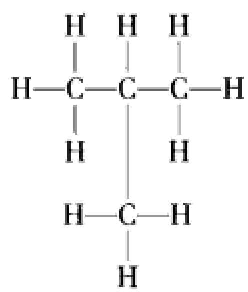
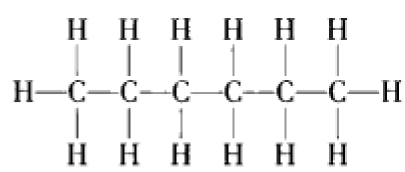
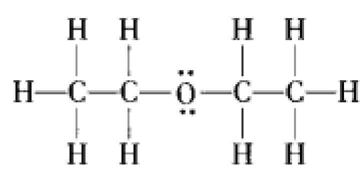
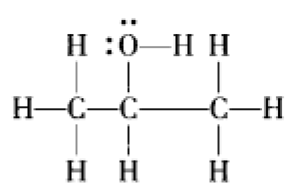
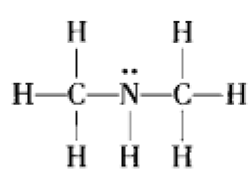
1−10 Structural Formulas

Several kinds of formulas are used by organic chemists to represent organic compounds. Some of these formulas involve a shorthand notation that requires some explanation. **Structural formulas** actually show which atoms are bonded to which. There are two types of structural formulas, complete Lewis structures and condensed structural formulas. In addition, there are several ways of drawing condensed structural formulas. As we have seen, a Lewis structure symbolizes a bonding pair of electrons as a pair of dots or as a dash (—). Lone pairs of electrons are shown as pairs of dots.

1-10A Condensed Structural Formulas

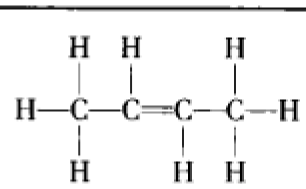
Condensed structural formulas (Table 1-2) are written without showing all the individual bonds. In a condensed structure, each central atom is shown together with the atoms that are bonded to it. The atoms bonded to a central atom are often listed after the central atom (as in CH_3CH_3 rather than $H_3C—CH_3$) even if that is not their actual bonding order. In many cases, if there are two or more identical groups, parentheses and a subscript may be used to represent all the identical groups. Nonbonding electrons are rarely shown in condensed structural formulas.

TABLE 1-2 Examples of Condensed Structural Formulas

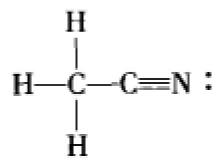
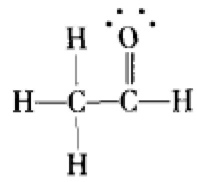
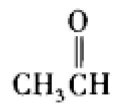
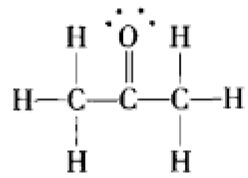
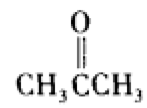
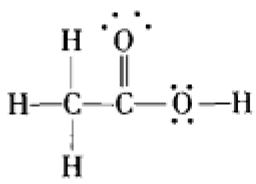
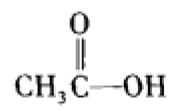
Compound	Lewis Structure	Condensed Structural Formula
isobutane (异丁烷)		$(CH_3)_3CH$
n-hexane (正己烷)		$CH_3(CH_2)_4CH_3$
diethyl ether (乙醚)		$CH_3CH_2OCH_2CH_3$ or $CH_3CH_2—O—CH_2CH_3$ or $(CH_3CH_2)_2O$
isopropyl alcohol (异丙醇)		$(CH_3)_2CHOH$
dimethylamine (二甲胺)		$(CH_3)_2NH$

When a condensed structural formula is written for a compound containing double or triple bonds, the multiple bonds are often drawn as they would be in a Lewis structure. Table 1-3 shows examples of condensed structural formulas containing multiple bonds. Notice that the —CHO group of an aldehyde and the —COOH group of a carboxylic acid are actually bonded differently from what the condensed notation suggests.

TABLE 1-3 Condensed Structural Formulas for Double and Triple Bonds

Compound	Lewis Structure	Condensed Structural Formula
2-butene (2-丁烯)		$CH_3CHCHCH_3$ or $CH_3CH{=}CHCH_3$

Continued

Compound	Lewis Structure	Condensed Structural Formula
acetonitrile（乙腈）		CH_3CN or $CH_3C{\equiv}N$
acetaldehyde（乙醛）		CH_3CHO or 
acetone（丙酮）		CH_3COCH_3 or 
acetic acid（乙酸）		CH_3COOH or  or CH_3CO_2H

PROBLEM 1-9

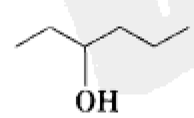
Draw complete Lewis structures for the following condensed structural formulas.

(a) $CH_3(CH_2)_3CH(CH_3)_2$　(b) $(CH_3)_2CHCH_2Cl$　(c) $CH_3CH_2COCHCH_2$
(d) CH_3CH_2CHO　(e) CH_3COCN　(f) $(CH_3)_3CCOOH$
(g) $(CH_3CH_2)_2CO$

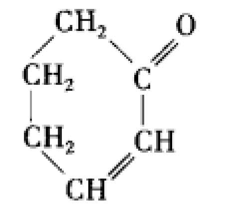
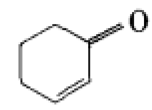
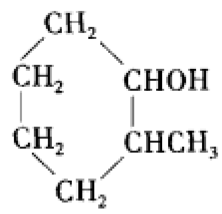
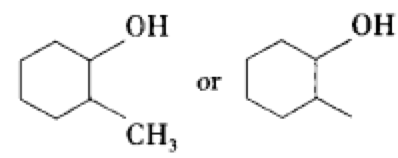
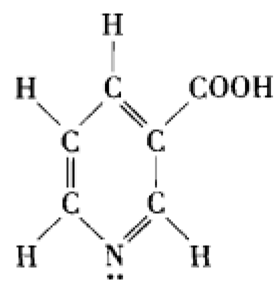
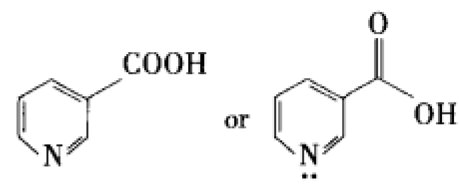
1-10B Line-Angle Formulas

Another kind of shorthand used for organic structures is the **line-angle formula**, sometimes called a **skeletal structure** or a **stick figure**. Line-angle formulas are often used for cyclic compounds and occasionally for noncyclic ones. In a stick figure, bonds are represented by lines, and carbon atoms are assumed to be present wherever two lines meet or a line begins or ends. Nitrogen, oxygen, and halogen atoms are shown, but hydrogen atoms are not usually drawn unless they are bonded to an atom that is drawn. Each carbon atom is assumed to have enough hydrogen atoms to give it a total of four bonds. Nonbonding electrons are rarely shown. Table 1-4 shows some examples of line-angle drawings.

TABLE 1-4 Examples of Line-Angle Drawings

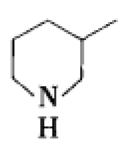
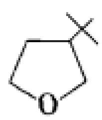
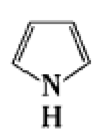
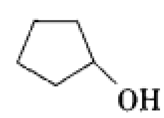
Compound	Condensed Structure	Line-Angle Formula
hexane（己烷）	$CH_3(CH_2)_4CH_3$	
2-hexene（2-己烯）	$CH_3CH{=}CHCH_2CH_2CH_3$	
3-hexanol（3-己醇）	$CH_3CH_2CH(OH)CH_2CH_2CH_3$	

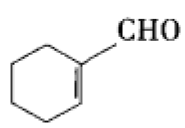
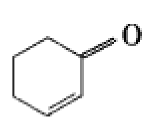
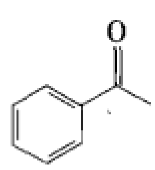
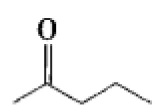
Continued

Compound	Condensed Structure	Line-Angle Formula
2-cyclohexenone (2-环己烯酮)		
2-methylcyclohexanol (2-甲基环己醇)		
nicotinic acid (烟酸) (a vitamin, also called niacin)		

PROBLEM 1-10

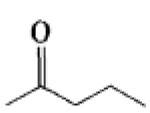
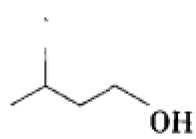
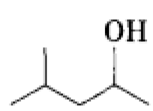
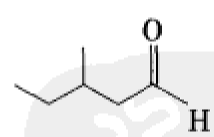
Give Lewis structures corresponding to the following line-angle structures.

(a)  (b)  (c)  (d) 

(e)  (f)  (g)  (h) 

PROBLEM 1-11

Draw condensed structural formulas corresponding to the following line-angle structures.

(a)  (b)  (c)  (d) 

1-11 Molecular Formulas and Empirical Formulas

Before we can write possible structural formulas for a compound, we need to know its molecular formula. The **molecular formula** simply gives the number of atoms of each element in one molecule of the compound. For example, the molecular formula for 1-butanol is $C_4H_{10}O$.

$$CH_3CH_2CH_2CH_2OH$$

1-butanol, molecular formula $C_4H_{10}O$

(1-丁醇)

Calculation of the Empirical Formula Molecular formulas can be determined by a two-step process. The first step is the determination of an **empirical formula**, simply the relative ratios of the elements present. Suppose,

for example, that an unknown compound was found by quantitative elemental analysis to contain 40.0% carbon and 6.67% hydrogen. The remainder of the weight (53.3%) is assumed to be oxygen. To convert these numbers to an empirical formula, we can follow a simple procedure.

1. Assume the sample contains 100 g, so the percent value gives the number of grams of each element. Divide the number of grams of each element by the atomic weight to get the number of moles of that atom in the 100-g sample.

2. Divide each of these numbers of moles by the smallest one. This step should give recognizable ratios.

For the unknown compound, we do the following computations:

$$\frac{40.0\ \text{g(C)}}{12.0\ \text{g/mol}} = 3.33\ \text{mol(C)};\quad \frac{3.33\ \text{mol}}{3.33\ \text{mol}} = 1$$

$$\frac{6.67\ \text{g(H)}}{1.01\ \text{g/mol}} = 6.60\ \text{mol(H)};\quad \frac{6.60\ \text{mol}}{3.33\ \text{mol}} = 1.98 \approx 2$$

$$\frac{53.3\ \text{g(O)}}{16.0\ \text{g/mol}} = 3.33\ \text{mol(O)};\quad \frac{3.33\ \text{mol}}{3.33\ \text{mol}} = 1$$

The first computation divides the number of grams of carbon by 12, the number of grams of hydrogen by 1, and the number of grams of oxygen by 16. We compare these numbers by dividing them by the smallest number, 3.33. The final result is a ratio of one carbon to two hydrogens to one oxygen. This result gives the empirical formula $C_1H_2O_1$ or CH_2O, which simply shows the ratios of the elements. The molecular formula can be any multiple of this empirical formula, because any multiple also has the same ratio of elements. Possible molecular formulas are CH_2O, $C_2H_4O_2$, $C_3H_6O_3$, $C_4H_8O_4$, etc.

Calculation of the Molecular Formula How do we know the correct molecular formula? We can choose the right multiple of the empirical formula if we know the molecular weight. Molecular weights can be determined by methods that relate the freezing-point depression or boiling-point elevation of a solvent to the molal concentration of the unknown. If the compound is volatile, we can convert it to a gas and use its volume to determine the number of moles according to the gas law. Nowadays *mass spectrometry* is often used for determination of molecular weights.

For our example (empirical formula CH_2O), let's assume that the molecular weight is determined to be about 60. The weight of one CH_2O unit is 30, so our unknown compound must contain twice this many atoms. The molecular formula must be $C_2H_4O_2$. The compound might be acetic acid.

In Chapters 12 and 13, we will use spectroscopic techniques to determine the complete structure for a compound once we know its molecular formula.

PROBLEM 1-12

Compute the empirical and molecular formulas for each of the following elemental analyses. In each case, propose at least one structure that fits the molecular formula.

	C	H	N	Cl	MW
(a)	40.0%	6.67%	0	0	90
(b)	32.0%	6.67%	18.7%	0	75
(c)	37.2%	7.75%	0	55.0%	64
(d)	38.4%	4.80%	0	56.8%	125

1-12 Arrhenius Acids and Bases

The properties and reactions of acids and bases are central to our study of organic chemistry. We need to consider

exactly what is meant by the terms **acid** and **base**. Most people would agree that H_2SO_4 is an acid and NaOH is a base. Is BF_3 an acid or a base? Is ethylene ($H_2C{=}CH_2$) an acid or a base? To answer these questions, we need to understand the three different definitions of acids and bases: the Arrhenius definition, the Brønsted-Lowry definition, and the Lewis definition.

Acidic compounds were first classified on the basis of their sour taste. The Latin terms *acidus* (sour) and *acetum* (vinegar) gave rise to our modern terms *acid* and *acetic acid*. Alkaline compounds (bases) were substances that neutralize acids, such as limestone and plant ashes (*al kalai* in Arabic).

The **Arrhenius** theory, developed at the end of the nineteenth century, defined acids as *substances that dissociate in water to give* H_3O^+ *ions*. The stronger acids, such as sulfuric acid (H_2SO_4), were assumed to dissociate to a greater degree than weaker acids, such as acetic acid (CH_3COOH).

$$\underset{\text{sulfuric acid (硫酸)}}{H_2SO_4} + H_2O \rightleftharpoons H_3O^+ + HSO_4^-$$

$$\underset{\text{acetic acid (乙酸)}}{CH_3{-}\overset{\overset{\large O}{\|}}{C}{-}OH} + H_2O \rightleftharpoons H_3O^+ + CH_3{-}\overset{\overset{\large O}{\|}}{C}{-}O^-$$

According to the Arrhenius definition, bases are *substances that dissociate in water to give hydroxide ions.* Strong bases, such as NaOH, were assumed to dissociate more completely than weaker, sparingly soluble bases such as $Mg(OH)_2$.

$$NaOH \rightleftharpoons Na^+ + {}^-OH$$

$$Mg(OH)_2 \rightleftharpoons Mg^{2+} + 2\ {}^-OH$$

The acidity or basicity of an aqueous (water) solution is measured by the concentration of H_3O^+. This value also implies the concentration of ^-OH because these two concentrations are related by the water ion-product constant:

$$K_w = [H_3O^+][{}^-OH] = 1.00 \times 10^{-14}\ (\text{at } 24\ ℃)$$

In a neutral solution, the concentrations of H_3O^+ and ^-OH are equal.

$$[H_3O^+] = [{}^-OH] = 1.00 \times 10^{-7}\ \text{mol/L in a neutral solution}$$

Acidic and basic solutions are defined by an excess of H_3O^+ or ^-OH.

$$\text{acidic: } [H_3O^+] > 10^{-7}\ \text{mol/L and } [{}^-OH] < 10^{-7}\ \text{mol/L}$$

$$\text{basic: } [H_3O^+] < 10^{-7}\ \text{mol/L and } [{}^-OH] > 10^{-7}\ \text{mol/L}$$

Because these concentrations can span a wide range of values, the acidity or basicity of a solution is usually measured on a logarithmic scale. The **pH** is defined as the negative logarithm (base 10) of the H_3O^+ concentration.

$$pH = -\lg[H_3O^+]$$

A neutral solution has a pH of 7, an acidic solution has a pH less than 7, and a basic solution has a pH greater than 7.

PROBLEM 1-13

Calculate the pH of the following solutions.

(a) 5.00 g of HBr in 100 mL of aqueous solution

(b) 1.50 g of NaOH in 50 mL of aqueous solution

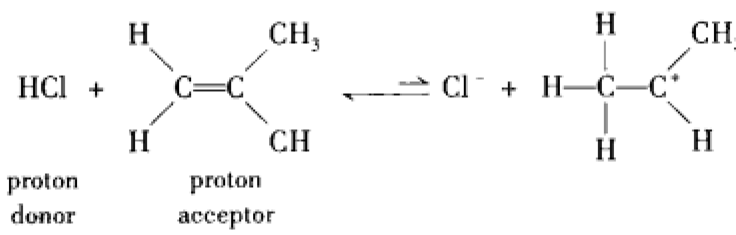
The Arrhenius definition was an important contribution to understanding many acids and bases, but it does not explain why a compound such as ammonia (NH_3) neutralizes acids, even though it has no hydroxide ion in its molecular formula. In Section 1−13 we discuss a more versatile theory of acids and bases that will include ammonia and a wider variety of organic acids and bases.

1−13 Brønsted-Lowry Acids and Bases

In 1923, Brønsted and Lowry defined acids and bases on the basis of the transfer of protons. A **Brønsted-Lowry acid** is *any species that can donate a proton*, and a **Brønsted-Lowry base** is *any species that can accept a proton.* These definitions also include all the Arrhenius acids and bases because compounds that dissociate to give H_3O^+ are proton donors, and compounds that dissociate to give ^-OH are proton acceptors. (Hydroxide ion accepts a proton to form H_2O.)

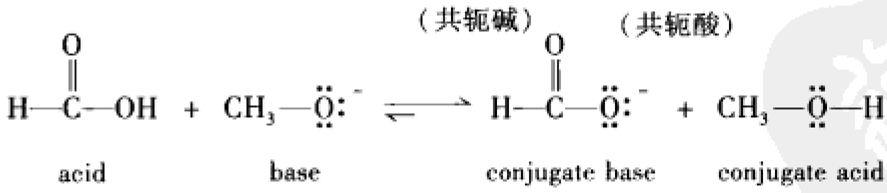
In addition to Arrhenius acids and bases, the Brønsted-Lowry definition includes bases that have no hydroxide ions, yet can accept protons. Consider the following examples of acids donating protons to bases. The NH_3 and $H_2C{=}CHCH_3$ are Brønsted-Lowry bases but not Arrhenius bases, because they have no hydroxide ions.

$$\underset{\substack{\text{proton donor}\\ \text{(质子给体)}}}{H_2SO_4} + \underset{\substack{\text{proton acceptor}\\ \text{(质子受体)}}}{:NH_3} \rightleftharpoons HSO_4^- + H{-}\overset{+}{N}H_3$$



When a base accepts a proton, it becomes an acid capable of returning that proton. When an acid donates its proton, it becomes a base capable of accepting that proton back. One of the most important principles of the Brønsted-Lowry definition is this concept of **conjugate acids and bases**. For example, NH_4^+ and NH_3 are a conjugate acid-base pair. NH_3 is the base; when it accepts a proton, it is transformed into its conjugate acid, NH_4^+. Many compounds (water, for instance) can react either as an acid or as a base. Here are some additional examples of conjugate acid-base pairs.

$$\underset{\text{acid}}{H_2O} + \underset{\text{base}}{:NH_3} \rightleftharpoons \underset{\substack{\text{conjugate base}\\ \text{(共轭碱)}}}{^-OH} + \underset{\substack{\text{conjugate acid}\\ \text{(共轭酸)}}}{NH_4^+}$$



1−13A Acid Strength

The strength of a Brønsted-Lowry acid is expressed as it is in the Arrhenius definition, by the extent of its ionization in water. The general reaction of an acid (HA) with water is the following:

$$\underset{\text{acid}}{HA} + H_2O \overset{K_a}{\rightleftharpoons} H_3O^+ + \underset{\text{base}}{A^-} \qquad K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

conjugate acid-base pair (共轭酸-碱对)

K_a is called the **acid-dissociation constant**, and its value indicates the relative strength of the acid. The stronger the acid, the more it dissociates, giving a larger value of K_a. Acid-dissociation constants vary over a wide range. Strong acids are almost completely ionized in water, and their dissociation constants are greater than 1. Most organic acids are weak acids, with K_a values less than 10^{-4}. Many organic compounds are extremely weak acids; for example, methane and ethane are essentially nonacidic, with K_a values less than 10^{-40}.

Because they span such a wide range, acid-dissociation constants are often expressed on a logarithmic scale. The pK_a of an acid is defined just like the pH of a solution: as the negative logarithm (base 10) of K_a.

$$pK_a = -\lg K_a$$

Strong acids generally have pK_a values around 0, and weak acids, such as most organic acids, have pK_a values that are greater than 4. *Weaker acids have larger* pK_a *values.* Table 1−5 lists K_a and pK_a values for some common inorganic and organic compounds. Notice that the pK_a values increase as the K_a values decrease.

TABLE 1−5 Relative Strength of Some Common Organic and Inorganic Acids and Their Conjugate Bases

	Acid		Conjugate Base		K_a	pK_a
strong acids (stronger)	HCl hydrochloric acid(氢氯酸,盐酸)	$+ H_2O \rightleftharpoons H_3O^+ +$	Cl^- chloride ion(氯离子)	weaker bases	1.6×10^{2}	−2.2
weak acids	HF hydrofluoric acid(氢氟酸)	$+ H_2O \rightleftharpoons H_3O^+ +$	F^- fluoride ion(氟离子)		6.8×10^{-4}	3.17
	H—C(=O)—OH formic acid(甲酸)	$+ H_2O \rightleftharpoons H_3O^+ +$	H—C(=O)—O^- formate ion(甲酸根离子)		1.7×10^{-4}	3.76
	CH_3—C(=O)—OH acetic acid(乙酸)	$+ H_2O \rightleftharpoons H_3O^+ +$	CH_3—C(=O)—O^- acetate ion(醋酸根离子)		1.8×10^{-5}	4.74
	H—C≡N: hydrocyanic acid(氢氰酸)	$+ H_2O \rightleftharpoons H_3O^+ +$	$^-$:C≡N: cyanide ion (氰负离子)		6.0×10^{-10}	9.22
	$^+NH_4$ ammonium ion(铵离子)	$+ H_2O \rightleftharpoons H_3O^+ +$	:NH_3 ammonia		5.8×10^{-10}	9.24
	CH_3—OH methyl alcohol (甲醇)	$+ H_2O \rightleftharpoons H_3O^+ +$	CH_3O^- methoxide ion(甲氧基负离子)		3.2×10^{-16}	15.5
	H_2O water	$+ H_2O \rightleftharpoons H_3O^+ +$	HO^- hydroxide ion(氢氧根离子)		1.8×10^{-16}	15.7
very weak	NH_3 ammonia(氨)	$+ H_2O \rightleftharpoons H_3O^+ +$	$^-$:$\ddot{N}H_2$ amide ion(氨基负离子)		10^{-33}	33
not acidic (weaker)	CH_4 methane(甲烷)	$+ H_2O \rightleftharpoons H_3O^+ +$	$^-$:CH_3 methyl anion (甲基负离子)	stronger bases	$<10^{-40}$	>40

PROBLEM 1−14

Ammonia appears in Table 1−5 both as an acid and as a conjugate base.

(a) Explain how ammonia can act as both an acid and a base. Which of these roles does it commonly fill in aqueous solutions?

(b) Show how water can serve as both an acid and a base.

(c) Show how methanol (CH_3OH) can serve as both an acid and a base. Write an equation for the reaction of methanol with sulfuric acid.

1−13B Base Strength

The strength of an acid is inversely related to the strength of its conjugate base. For an acid (HA) to be strong, its conjugate base (A^-) must be stable in its anionic form; otherwise, HA would not easily lose its proton. Therefore, the conjugate base of a strong acid must be a weak base. On the other hand, if an acid is weak, its conjugate is a strong base.

$$\underset{\text{strong acid}}{HCl} + H_2O \rightleftharpoons H_3O^+ + \underset{\text{weak base}}{Cl^-}$$

$$\underset{\text{weak acid}}{CH_3-\ddot{\underset{..}{O}}H} + H_2O \rightleftharpoons H_3O^+ + \underset{\text{strong base}}{CH_3\ddot{\underset{..}{O}}:^-}$$

In the reaction of an acid with a base, the equilibrium generally favors the *weaker* acid and base. For example, in the preceding reactions, H_3O^+ is a weaker acid than HCl but a stronger acid than CH_3OH. It also follows that H_2O is a stronger base than Cl^- but a weaker base than CH_3O^-.

The strength of a base is measured much like the strength of an acid, by using the equilibrium constant of the hydrolysis reaction.

$$\underset{\substack{\text{conjugate}\\\text{base}}}{A^-} + H_2O \overset{K_b}{\rightleftharpoons} \underset{\substack{\text{conjugate}\\\text{acid}}}{HA} + {}^-OH$$

The equilibrium constant (K_b) for this reaction is called the *base-dissociation constant* for the base A^-. Because this constant spans a wide range of values, it is often given in logarithmic form. The negative logarithm (base 10) of K_b is defined as pK_b.

$$K_b = \frac{[HA][{}^-OH]}{[A^-]} \qquad pK_b = -\lg K_b$$

The product of K_a and K_b must always equal the ion-product constant of water, 10^{-14}. If the value of K_a is large, the value of K_b must be small; that is, the stronger an acid, the weaker its conjugate base. The weaker an acid, the stronger its conjugate base. Acid-base reactions favor the weaker acid and the weaker base.

PROBLEM 1−15 (PARTIALLY SOLVED)

Write equations for the following acid-base reactions. Use the information in Table 1−5 to predict whether the equilibrium will favor the reactants or the products.

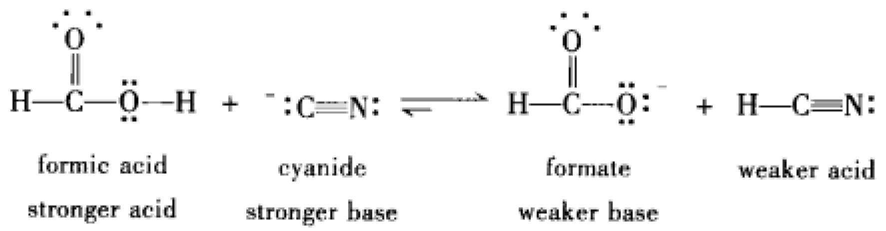
(a) $HCOOH + {}^-CN$ **(b)** $CH_3COO^- + CH_3OH$

(c) $CH_3OH + NaNH_2$ **(d)** $NaOCH_3 + HCN$

(e) $HCl + H_2O$ **(f)** $H_3O^+ + CH_3O^-$

SOLUTION TO (a)

Cyanide is the conjugate base of HCN. It can accept a proton from formic acid:



Reading from Table 1-5, formic aicd ($pK_a = 3.76$) is a stronger acid than HCN($pK_a = 9.22$), and cyanide is a stronger base than formate. The products (weaker acid and base) are favored.

PROBLEM 1-16

Each of the following compounds can act as an acid. Show the reaction of each compound with a general base (A^-), and show the Lewis structure of the conjugate base that results.

(a) CH_3CH_2OH (b) CH_3NH_2 (c) CH_3COOH

PROBLEM 1-17

Each of the compounds in Problem 1-16 can also react as a base. Show the reaction of each compound with a general acid (HA), and show the Lewis structure of the conjugate acid that results.

PROBLEM 1-18

Problem 1-17 showed protonation of the double-bonded oxygen in acetic acid. Show the product of protonation on the other (—OH) oxygen. Explain why protonation of the double-bonded oxygen is favored.

1-13C Structural Effects on Acidity

How can we look at a structure and predict whether a compound will be a strong acid, a weak acid, or not an acid at all? To be a Brønsted-Lowry acid (HA), a compound must contain a hydrogen atom that can be lost as a proton. A strong acid must have a stable conjugate base ($A:^-$) after losing the proton.

The stability of the conjugate base is a good guide to acidity. More stable anions tend to be weaker bases, and their conjugate acids tend to be stronger acids. Some of the factors that affect the stability of conjugate bases are electronegativity, size and resonance.

Electronegativity A more electronegative element bears a negative charge more easily, giving a more stable conjugate base and a stronger acid. Electronegativities increase from left to right in the periodic table:

Electronegativity C < N < O < F

electronegativity increases →

Stability $^-CH_3 < {}^-NH_2 < {}^-OH < {}^-F$

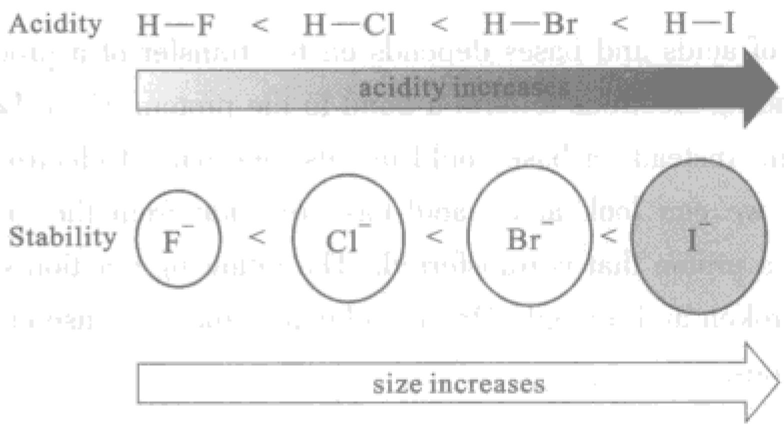
Acidity $H—CH_3 < H—NH_2 < H—OH < H—F$

acidity increases →

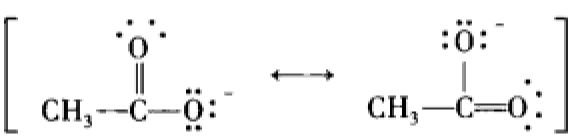
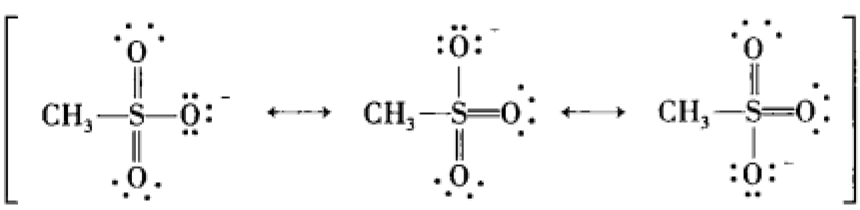
Basicity $^-CH_3 > {}^-NH_2 > {}^-OH > {}^-F$

← basicity increases

Size The negative charge of an anion is more stable if it is spread over a larger region of space. Within a column of the periodic table, acidity increases down the column, as the size of the elements increases.



Resonance Stabilization The negative charge of a conjugate base may be delocalized over two or more atoms by resonance. Depending on how electronegative those atoms are, and how many share the charge, resonance delocalization is often the dominant effect helping to stabilize an anion. Consider the following conjugate bases.

Conjugate Base	Acid	pK_a
$CH_3CH_2—\ddot{O}:^-$ ethoxide ion(乙氧基负离子)	$CH_3CH_2—OH$ ethanol(乙醇)	15.9 (weak aicd)
 acetate ion(乙酸根离子)	$CH_3—C(=O)—OH$ acetic acid(乙酸)	4.74 (moderate acid)
 methanesulfonate ion(甲磺酸根离子)	$CH_3—S(=O)_2—OH$ methanesulfonic acid(甲磺酸)	-1.2 (strong acid)

Ethoxide ion is the strongest of these three bases. Ethoxide has a negative charge localized on one oxygen atom; acetate ion has the negative charge shared by two oxygen atoms; and the methanesulfonate ion has the negative charge spread over three oxygen atoms. The pK_a values of the conjugate acids of these anions show that acids are stronger if they deprotonate to give resonance-stabilized conjugate bases.

PROBLEM 1-19

Write equations for the following acid-base reactions. Label the conjugate acids and bases, and show any resonance stabilization. Predict whether the equilibrium favors the reactants or products.

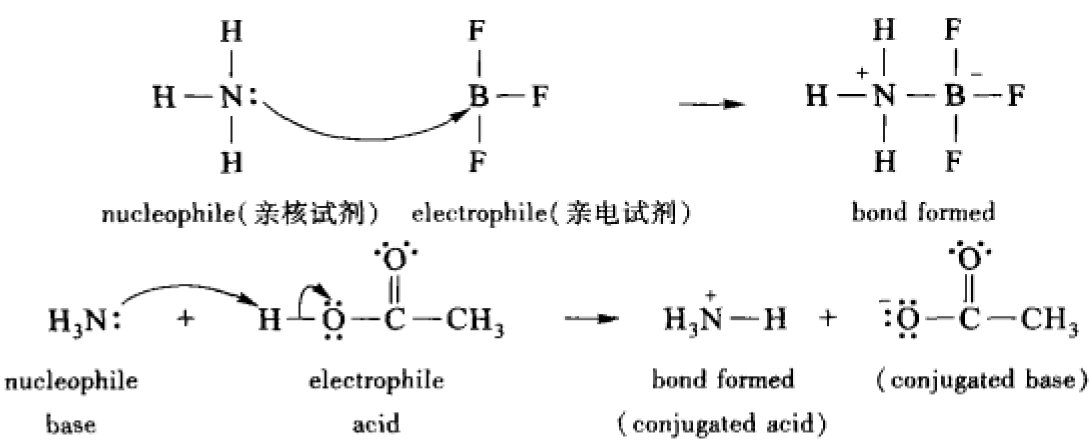
(a) $CH_3CH_2OH + CH_3NH^-$
(b) $CH_3CH_2COOH + CH_3NHCH_3$
(c) $CH_3OH + H_2SO_4$
(d) $NaOH + H_2S$
(e) $CH_3NH_3^+ + CH_3O^-$
(f) $CH_3O^- + CH_3COOH$
(g) $CH_3SO_3^- + CH_3COOH$

1–14 Lewis Acids and Bases

The Brønsted-Lowry definition of acids and bases depends on the transfer of a proton from the acid to the base. The base uses a pair of nonbonding electrons to form a bond to the proton. G. N. Lewis reasoned that this kind of reaction does not need a proton. Instead, a base could use its lone pair of electrons to bond to some other electron-deficient atom. In effect, we can look at an acid-base reaction from the viewpoint of the *bonds* that are formed and broken rather than a proton that is transferred. The following reaction shows the proton transfer, with emphasis on the bonds being broken and formed. Organic chemists routinely use curved arrows to show the movement of the participating electrons.

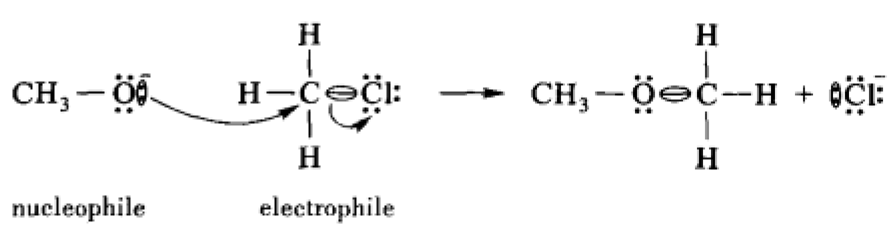
Lewis bases are species with nonbonding electrons that can be donated to form new bonds. **Lewis acids** are species that can accept these electron pairs to form new bonds. Since a Lewis acid *accepts* a pair of electrons, it is called an **electrophile**, from the Greek words meaning "lover of electrons". A Lewis base is called a **nucleophile**, or "lover of nuclei", because it donates electrons to a nucleus with an empty (or easily vacated) orbital.

The Lewis acid-base definitions include reactions having nothing to do with protons. Following are some examples of Lewis acid-base reactions. Notice that the common Brønsted-Lowry acids and bases also fall under the Lewis definition, with a proton serving as the electrophile. Curved arrows are used to show the movement of electrons, generally from the nucleophile to the electrophile.



Some of the terms associated with acids and bases have evolved specific meanings in organic chemistry. When organic chemists use the term *base*, they usually mean a proton acceptor (a Brønsted-Lowry base). Similarly, the term *acid* usually means a proton donor (a Brønsted-Lowry acid). When the acid-base reaction involves formation of a bond to some other element (especially carbon), organic chemists refer to the electron donor as a *nucleophile* (Lewis base) and the electron acceptor as an *electrophile* (Lewis acid).

The **curved-arrow formalism** is used to show the flow of an electron pair *from the electron donor to the electron acceptor.* The movement of each pair of electrons involved in making or breaking bonds in indicated by its own separate arrow, as shown in the preceding set of reactions. In the preceding reaction of CH_3O^- with CH_3Cl, one curved arrow shows the lone pair on oxygen forming a bond to carbon. Another curved arrow shows that the C—Cl bonding pair detaches from carbon and becomes a lone pair on the Cl^- product.

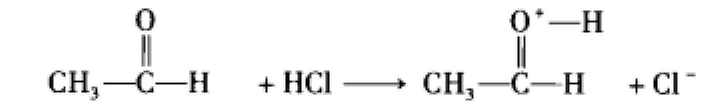


The curved-arrow formalism is universally used for keeping track of the flow of electrons in reactions. We have also used this device to keep track of electrons in resonance structures as we imagined their "flow" in going from one resonance structure to another. Remember that electrons do not "flow" in resonance structures: They are simply delocalized. Still, the curved-arrow formalism helps our *minds* flow from one resonance structure to another. We will find ourselves constantly using these curved arrows to keep track of electrons, both as reactants change to products and as we imagine additional resonance structures of a hybrid.

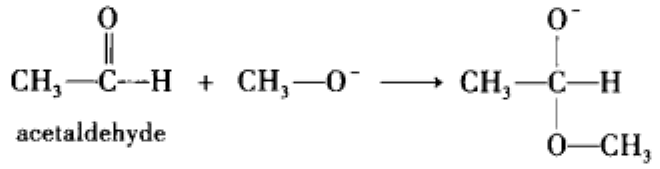
PROBLEM 1-20 (PARTIALLY SOLVED)

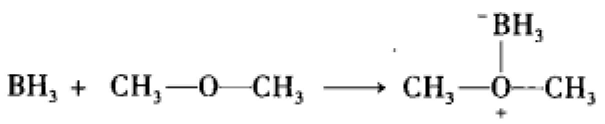
In the following acid-base reactions,

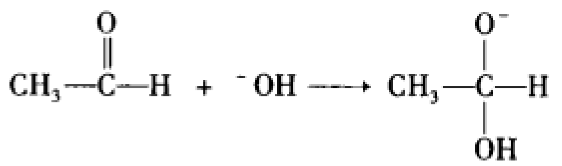
1. determine which species are acting as electrophiles (acids) and which are acting as nucleophiles (bases).
2. use the curved-arrow formalism to show the movement of electron pairs in these reactions, as well as the imaginary movement in the resonance hybrids of the products.
3. indicate which reactions are best termed Brønsted-Lowry acid-base reactions.

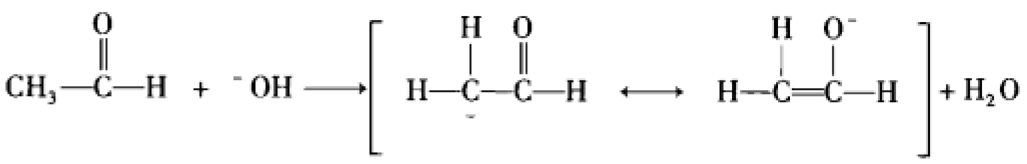
(a) 

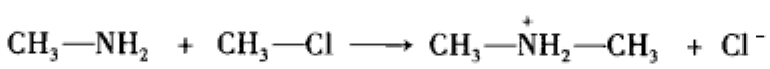
acetaldehyde(乙醛)

(b) 

(c) 

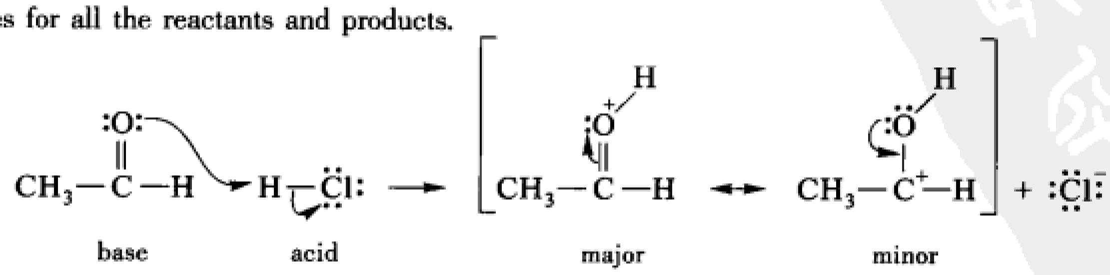
(d) 

(e) 

(f) 

SOLUTION TO (a)

This reaction is a proton transfer from HCl to the C=O group of acetaldehyde. Therefore, it is a Brønsted-Lowry acid-base reaction, with HCl acting as the acid (proton donor) and acetaldehyde acting as the base (proton acceptor). Before drawing any curved arrows, remember that arrows must show the movement of electrons *from* the electron-pair donor (the base) *to* the electron-pair acceptor (the acid). An arrow must go *from* the electrons on acetaldehyde that form the bond *to* the hydrogen atom, and the bond to chlorine must break, with the chloride ion taking these electrons. Drawing these arrows is easier once we draw good Lewis structures for all the reactants and products.



The resonance forms of the product show that a pair of electrons can be moved between the oxygen atom and the C=O pi bond. The positive charge is delocalized over the carbon and oxygen atoms, with most of the positive charge on oxygen because all octets are satisfied in that resonance structure.

Summary in Chinese

本 章 概 要

一、原子轨道与电子构型(atomic orbitals and electronic structure,第 1~3 周期原子)

1. 原子轨道类型:*s* 轨道(球形),*p* 轨道(哑铃形,用“+”和“-”号标记轨道两瓣,表示波相相反)。

2. 原子轨道能量:$1s<2s<2p_x=2p_y=2p_z<3s<3p_x=3p_y=3p_z$。能量相同的轨道称为简并轨道(degenerate orbitals)。

3. 原子的电子构型(电子排布原则):

- 能量最低原理:电子尽可能占据能量最低的轨道。
- 泡利不相容原理:每个轨道只能容纳两个自旋相反的电子(↑↓)。
- 洪德规则:对于简并轨道,首先每个轨道填充一个电子,自旋平行,待每个简并轨道均被一个电子占据后,才可填入第二个电子,与第一个电子自旋相反。

二、化学键(chemical bonds)

1. 八电子规则(the octet rule):除氢原子外,其他原子各电子层的轨道充满电子形成与惰性气体氦或氩相同的电子构型才是稳定的。因此,原子通过转移或共用电子达到价电子层八电子的稳定电子构型。

2. 化学键
   - 离子键(ionic bond)
     两原子之间电子转移形成两个带相反电荷的离子,静电相互作用形成离子键
   - 共价键(covalent bond)
     两原子共用一对电子形成共价键
     - 非极性共价键 (non-polar covalent bond)
     - 极性共价键 (polar covalent bond)

碳原子为 4 价,能与另一碳原子或其他原子形成共价单键(single bond)、双键(double bond)(C═C,C═X,X=O,S,N)和三键(triple bond)(—C≡C—,—C≡N)。单键被称为饱和键,双键和三键被称为不饱和键。

3. 其他重要基本概念:

- 化合价(valence):原子形成化学键的数目,由原子最外层价电子的数目及性质决定。
- 价电子(valence electrons):排布在原子最外层的电子。
- 非键电子(non-bonding electrons):未成键的价电子称为非键电子,未成键的电子对称为孤对电子(lone pair electrons)。
- 电负性(electronegativity):电负性表示原子实(原子核+非价电子)对价电子的吸引能力,电负性大的元素吸引电子的能力强。电负性与外界条件无关,是每种元素固有的性质。但同一元素的电负性随杂化状态不同会发生明显变化,原子的杂化轨道(Section 2-4)中含 *s* 轨道成分越多,其电负性越大。
- 形式电荷(formal charge):用来示意电荷在极性键或极性分子中的分布。可用下式计算:形式电荷(FC)=原子族数-非键电子数-1/2 共用电子数。

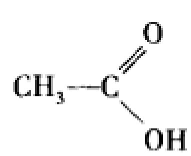
三、构造式(structural formulas)

1. 实验式(empirical formula):仅给出化合物中不同元素的比例,如 C_nH_{2n}、$C_nH_{2n}O_n$ 等。

2. 分子式(molecular formula):给出化合物中不同元素的准确组成,如 C_4H_8、$C_2H_4O_2$ 等。

3. 构造式(structural formula):不仅给出化合物中不同元素的准确组成,而且表示出分子中原子的成键顺序和方式,如:

CH_3—CH_2—CH═CH_2



在不需要表明分子立体结构的情况下，分子的构造式一般用路易斯构造式（Lewis structure formula）表示，或用缩简构造式（condensed structure formula）和键线－角构造式（line-angle formula）表示。

四、共振论（resonance theory）

1. 共振结构（resonance structure）与共振杂化体（resonance hybrid）：电子离域体系的分子、离子或自由基的电子或电荷分布不能用一种路易斯构造式表示清楚，必须用两种或多种原子核位置不变、只是价电子排布不同的路易斯构造式表示，这些路易斯构造式称为共振结构或共振式（resonance form）。实际分子、离子或自由基的真正结构是所有可能的共振结构的共振杂化体。化学家用共振结构直观地表明价电子在整个分子中的离域现象。共振杂化体的能量低于任何一个共振结构的能量。

2. 共振能（resonance energy）：一个电子离域体系的最稳定的共振结构的能量与其共振杂化体的能量差称为共振能。共振效应使共振杂化体稳定，能够写出的共振式数目越多，其杂化体就越稳定。

3. 共振式的书写规则：在所有共振式中，原子核的位置必须保持不变，只有共振轨道上的电子转移；所有共振式必须具有同样的电子数、总电荷数和未成对电子数。例如，烯丙基碳自由基的共振结构可表示为：

$$CH_3—\dot{C}H—CH{=}CH_2 \longleftrightarrow CH_3—CH{=}CH—\dot{C}H_2$$

4. 判断共振结构相对稳定性要点：原子价电子层是否符合八电子规则；形式电荷的数目和位置（考虑带电荷原子的电负性）；电荷间的相互作用。越稳定的共振结构对共振杂化体的贡献越大，电子离域体系的真实结构更像最稳定的共振结构。

五、酸碱理论（acid-base theory）

1. 阿仑尼乌斯（Arrhenius）理论：能在水中解离出 H_3O^+ 离子的物种为酸，能在水中解离出 OH^- 离子的物种为碱。这种酸碱理论有很大的局限性，在有机化学中常用质子酸碱和电子酸碱理论来解释化合物的酸碱性质和反应。

2. 布朗斯特－劳尔（Brønsted-Lowry）理论（质子酸碱理论）：能给出质子的物质为酸，酸给出质子后生成的分子或离子称为该酸的共轭碱（conjugate base）；能接受质子的物种为碱，碱接受质子后生成的分子或离子称为该碱的共轭酸（conjugate acid）。强酸的共轭碱为弱碱，强碱的共轭酸为弱酸，反之亦然。用酸解离常数（acid-dissociation constant，K_a 或 pK_a）或碱解离常数（base-dissociation constant，K_b 或 pK_b）定量衡量化合物和离子的酸碱性强弱。酸碱反应平衡总是趋向生成弱酸、弱碱。

3. 路易斯（Lewis）理论（电子酸碱理论）：能接受电子对的物种为酸，酸为亲电试剂（electrophile）；能给出电子对的物种为碱，碱为亲核试剂（nucleophile）。电子酸碱理论扩大了酸碱范围，又称为广义酸碱理论。

4. 影响有机酸酸性的主要因素：对于同一周期的原子，考虑氢所键合的原子的电负性，电负性越强，氢的酸性越强；对于同一族的原子，考虑氢所键合原子的大小，原子半径越大，氢的酸性越强。此外，还需要考虑取代基的诱导效应、能否生成分子内氢键、氢所键合的原子的轨道杂化形式（sp、sp^2 或 sp^3）以及共振效应对酸的共轭碱的稳定化作用等因素。

Essential Problem-Solving Skills in Chapter 1

1. Draw and interpret Lewis, condensed, and line-angle structural formulas. Show which atoms bear formal charges.
2. Draw resonance forms, and use them to predict stabilities.
3. Calculate empirical and molecular formulas from elemental compositions.
4. Predict relative acidities and basicities based on structure, bonding, and resonance of conjugate acid-base pairs.
5. Calculate, use, and interpret values of K_a and pK_a.

6. Identify nucleophiles (Lewis bases) and electrophiles (Lewis acids), and write equations for Lewis acid-base reactions using curved arrows to show the flow of electrons.

Study Problems

The best way to learn organic chemistry is to use it. You will certainly need to read and reread all the material in the chapter, but this level of understanding is just the beginning. Problems are provided so you can work with the ideas, applying them to new compounds and new reactions that you have never seen before. By working problems, you force yourself to use the material and fill in the gaps in your understanding. You also increase your level of self-confidence and your ability to do well on exams.

Several kinds of problems are included in each chapter. There are problems within the chapters, providing examples and drill for the material as it is covered. Work these problems as you read through the chapter to ensure your understanding as you go along. Answers to many of these in-chapter problems are found at the back of this book. Study Problems at the end of each chapter give you additional experience using the material, and they force you to think in depth about the ideas. Problems with stars (*) are more difficult problems that require extra thought and perhaps some extension of the material presented in the chapter. Some of the study problems have short answers in the back of this book, and all of them have detailed answers in the accompanying Solutions Manual.

Taking organic chemistry without working the problems is like skydiving without a parachute. Initially there is a breezy sense of freedom and daring. But then, there is the inevitable jolt that comes at the end for those who went unprepared.

1-21 Define and give an example for each term.

(a) isotopes (同位素) (b) orbital (轨道) (c) node (节点)
(d) degenerate orbitals (简并轨道) (e) valence electrons (价电子) (f) ionic bonding (离子键合)
(g) covalent bonding (共价键合) (h) Lewis structure (i) nonbonding electrons (非键电子)
(j) single bond (单键) (k) double bond (双键) (l) triple bond (三键)
(m) polar bond (极性键) (n) formal charges (形式电荷) (o) resonance forms (共振式)
(p) molecular formula (分子式) (q) empirical formula (经验式) (r) Arrhenius acid and base
(s) Brønsted-Lowry acid and base (t) Lewis acid and base (u) electrophile (亲电试剂)
(v) nucleophile (亲核试剂)

1-22 Name the element that corresponds to each electronic configuration.

(a) $1s^2 2s^2 2p^2$ (b) $1s^2 2s^2 2p^4$ (c) $1s^2 2s^2 2p^6 3s^2 3p^3$ (d) $1s^2 2s^2 2p^6 3s^2 3p^5$

1-23 (a) Both PCl_3 and PCl_5 are stable compounds. Draw Lewis structures for these two compounds.

(b) NCl_3 is a known compound, but all attempts to synthesize NCl_5 have failed. Draw Lewis structures for NCl_3 and a hypothetical NCl_5, and explain why NCl_5 is an unlikely structure.

1-24 Draw a Lewis structure for each compound. Include all nonbonding pairs of electrons.

(a) $CH_3CHCHCH_2CHCHCOOH$ (b) $NCCH_2COCH_2CHO$
(c) $CH_2CHCH(OH)CH_2CO_2H$ (d) $CH_3CH(CH_3)CH_2C(CH_2CH_3)_2CHO$

1-25 Draw a line-angle formula for each compound in Problem 1-24.

1-26 Draw a complete structural formula and a condensed structural formula for

(a) three compounds of formula C_3H_8O (b) five compounds of formula C_3H_6O

1-27 Compound X, isolated from lanolin (sheep's wool fat), has the pungent aroma of dirty sweatsocks. A careful analysis showed that compound X contains 62.0% carbon and 10.4% hydrogen. No nitrogen or halogen was found.

(a) Compute an empirical formula for compound X.

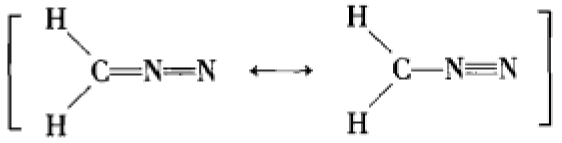
(b) A molecular weight determination showed that compound X has a molecular weight of approximately 117. Find the mo-

lecular formula of compound X.

(c) There are many possible structures that have this molecular formula. Draw complete structural formulas for four of them.

1-28 For each of the following structures,

1. Draw a Lewis structure; fill in any nonbonding electrons.
2. Calculate the formal charge on each atom other than hydrogen. All are electrically neutral except as noted.

(a) 

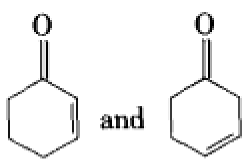
(b) $(CH_3)_3NO$ (trimethylamine oxide) (三甲基氧化胺)

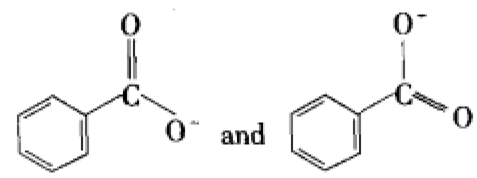
(c) $[\ CH_2{=}CH{-}CH_2\ ]^+$

(d) CH_3NO_2

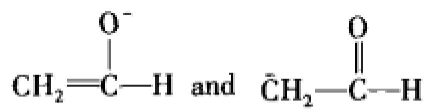
(e) $[(CH_3)_3O]^+$

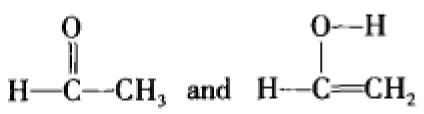
1-29 Determine whether the following pairs of structures are actually different compounds or simply resonance forms of the same compounds.

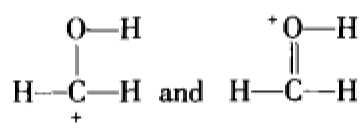
(a) 

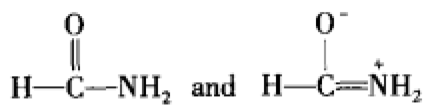
(b) 

(c)

(d) 

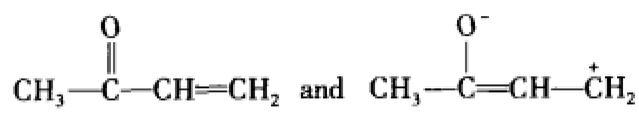
(e) 

(f) 

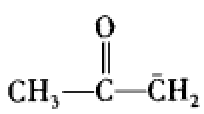
(g) 

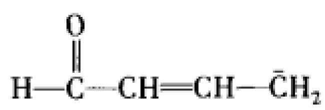
(h) $CH_2{=}C{=}O$ and $H{-}C{\equiv}C{-}OH$

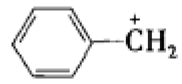
(i) $CH_2{=}CH{-}\overset{+}{C}H_2$ and $\overset{+}{C}H_2{-}CH{=}CH_2$

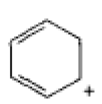
(j) 

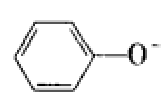
1-30 Draw the important resonance forms to show the delocalization of charges in the following ions.

(a) 

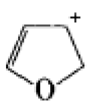
(b) 

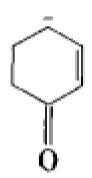
(c) 

(d) 

(e) 

(f)

(g) 

(h) 

(i) $CH_3{-}CH{=}CH{-}CH{=}CH{-}\overset{+}{C}H{-}CH_3$

(j) $CH_3{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}\overset{+}{C}H_2$

1-31 (a) Draw the resonance forms for SO_2 (bonded O—S—O)

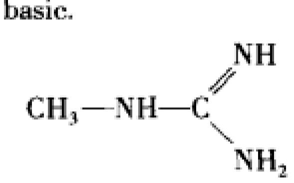
(b) Draw the resonance forms for ozone (bonded O—O—O)

(c) Sulfur dioxide has one more resonance form than ozone. Explain why this structure is not possible for ozone.

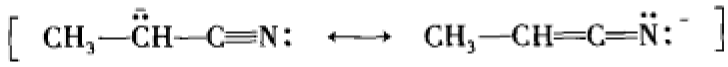
***1-32** The following compound can become protonated on any of the three nitrogen atoms. One of these nitrogens is much more basic than the others, however.

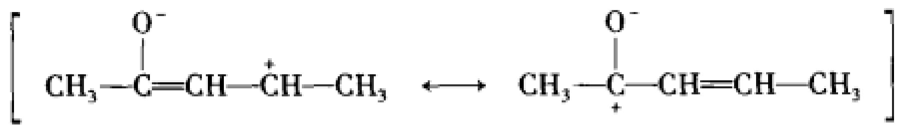
(a) Draw the important resonance forms of the products of protonation on each of the three nitrogen atoms.

(b) Determine which nitrogen atom is the most basic.



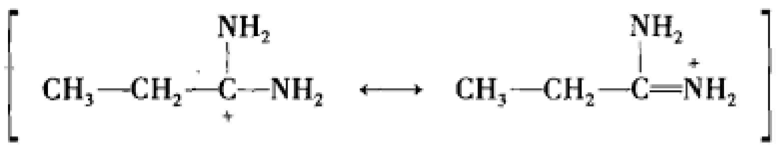
1−33 In the following sets of resonance forms, label the major and minor contributors and state which structures would be of equal energy. Add any missing resonance forms.

(a) 

(b) 

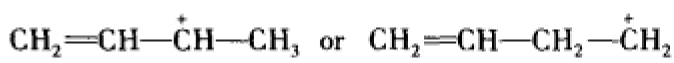
(c)

(d)

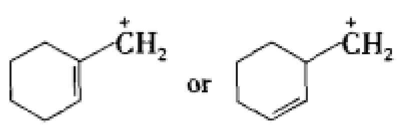
(e) 

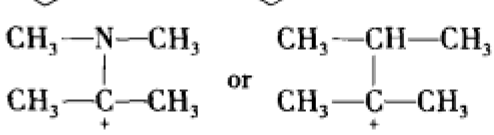
1−34 For each pair of ions, determine which ion is more stable. Use resonance forms to explain your answers.

(a)

(b) 

(c)

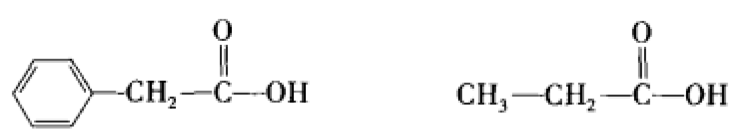
(d) 

(e) 

1−35 Rank the following species in order of increasing basicity. Explain your reasons for ordering them as you do.

CH_3O^- H_2O CH_3COO^- NaOH HF NH_2^- HSO_4^-

1−36 The K_a of phenylacetic acid is 5.2×10^{-5}, and the pK_a of propionic acid is 4.87.

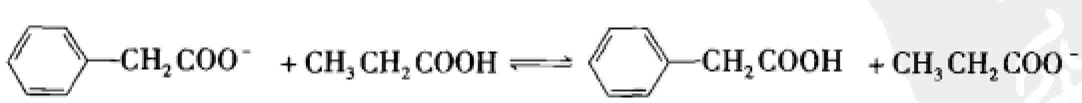


phenylacetic acid, $K_a = 5.2 \times 10^{-5}$ (苯基乙酸) propionic acid, pK_a = 4.87 (丙酸)

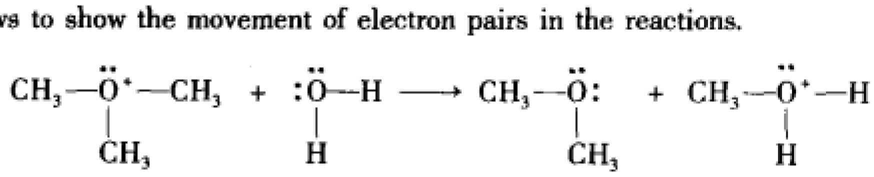
(a) Calculate the pK_a of phenylacetic acid and the K_a of propionic acid.

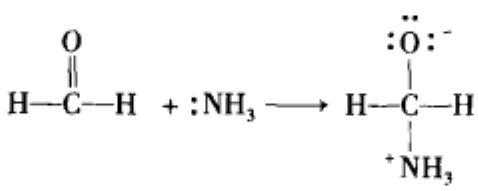
(b) Which of these is the stronger acid? Calculate how much stronger an acid it is.

(c) Predict whether the following equilibrium will favor the reactants or the products.



1−37 Label the reactants in these acid-base reactions as Lewis acids (electrophiles) or Lewis bases (nucleophiles). Use curved arrows to show the movement of electron pairs in the reactions.

(a) 

(b) 

(c) $CH_3-\ddot{N}H_2 + CH_3-CH_2-\ddot{\underset{..}{Cl}}: \longrightarrow CH_3-\overset{+}{N}H_2-CH_2CH_3 + :\ddot{\underset{..}{Cl}}:^-$

(d) $CH_3-\overset{\overset{\ddot{O}}{\|}}{C}-CH_3 + H_2SO_4 \longrightarrow CH_3-\overset{\overset{\dot{O}^+-H}{\|}}{C}-CH_3 + HSO_4^-$

(e) $(CH_3)_3CCl + AlCl_3 \longrightarrow (CH_3)_3C^+ + {}^-AlCl_4$

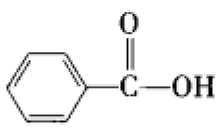
(f) $CH_2{=}CH_2 + BF_3 \longrightarrow \overset{-}{B}F_3-CH_2-\overset{+}{C}H_2$

(g) $\overset{-}{B}F_3-CH_2-\overset{+}{C}H_2 + CH_2{=}CH_2 \longrightarrow \overset{-}{B}F_3-CH_2-CH_2-CH_2-\overset{+}{C}H_2$

1-38 Predict the products of the following acid-base reactions.

(a) $H_2SO_4 + CH_3COO^- \rightleftharpoons$

(b) $CH_3COOH + (CH_3)_3N: \rightleftharpoons$

(c)  $+ {}^-OH \rightleftharpoons$

(d) $(CH_3)_3\overset{+}{N}H + {}^-OH \rightleftharpoons$

(e) $HO-\overset{\overset{O}{\|}}{C}-OH + 2\,{}^-OH \rightleftharpoons$

(f) $H_2O + NH_3 \rightleftharpoons$

(g) $HCOOH + CH_3O^- \rightleftharpoons$

*1-39 Methyllithium (CH_3Li) is often used as a base in organic reactions.

(a) Predict the products of the following acid-base reaction.

$$CH_3CH_2-OH + CH_3-Li \longrightarrow$$

(b) What is the conjugate acid of CH_3Li? Would you expect CH_3Li to be a strong base or a weak base?

Chapter 2

Structure and Properties of Organic Molecules

In Chapter 1, we considered how atoms bond together to gain noble-gas configurations, forming molecules in the process. Using the octet rule, we drew Lewis structures for organic molecules and used these diagrams to determine which bonds are single bonds, double bonds, and triple bonds. We discussed various ways of drawing organic structures, and we saw how resonance structures represent molecules whose actual bonding cannot be described by a single Lewis structure.

Chapter 1 does not explain the actual shapes and properties of organic molecules. To understand these aspects of molecular structure we need to consider how the atomic orbitals on an atom mix to form *hybrid atomic orbitals* and how orbitals on different atoms combine to form *molecular orbitals*. In this chapter, we look more closely at how combinations of orbitals account for the shapes and properties we observe in organic molecules.

2-1 Wave Properties of Electrons in Orbitals

We like to picture the atom as a miniature solar system, with the electrons orbiting around the nucleus. This solar system picture satisfies our intuition, but it does not accurately reflect today's understanding of the atom. About 1923, Louis de Broglie suggested that the properties of electrons in atoms are better explained by treating the electrons as waves rather than as particles.

There are two general kinds of waves, *traveling waves* and *standing waves*. Examples of traveling waves are the sound waves that carry a thunderclap and the water waves that form the wake of a boat. Standing waves vibrate in a fixed location. Standing waves are found inside an organ pipe, where the rush of air creates a vibrating air column, and in the wave pattern of a guitar string when it is plucked. An electron in an atomic orbital is like a stationary, bound vibration: a standing wave.

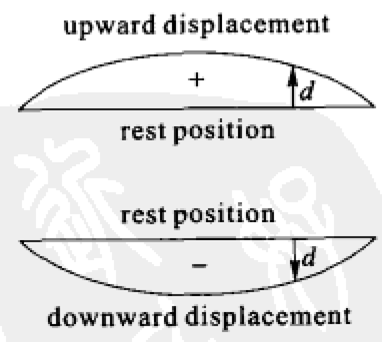


Figure 2−1 A standing wave. The fundamental frequency of a guitar string is a standing wave with the string alternately displaced upward and downward.

To understand the features of an orbital (a three-dimensional standing wave) more easily, let's consider the vibration of a guitar string as a one-dimensional analogy (see Figure 2−1). If you pluck a guitar string at its middle, a standing wave results. In this mode of vibration, all of the string is displaced upward for a fraction of a second, then downward for an equal time. An instantaneous picture of the waveform shows the string displaced in a smooth curve either upward or downward, depending on the exact instant of the picture.

The waveform of a 1*s* orbital is like this guitar string, except that it is three-dimensional. The orbital can be described by its **wave function**, ψ, which is the mathematical description of the shape of the wave as it vibrates. All of the wave is positive in sign for a brief instant; then it is negative in sign. The electron density at any point is given by ψ^2, the square of the wave function at that point. *Notice that the plus sign and the minus sign of these wave functions are not charges. The plus or minus sign is the instantaneous sign of the constantly changing wave function.* The 1*s* orbital is spherically symmetrical, and it is often represented by a circle (representing a sphere) with a nucleus in the center and with a plus or minus sign to indicate the instantaneous sign of the wave function (Figure 2−2).

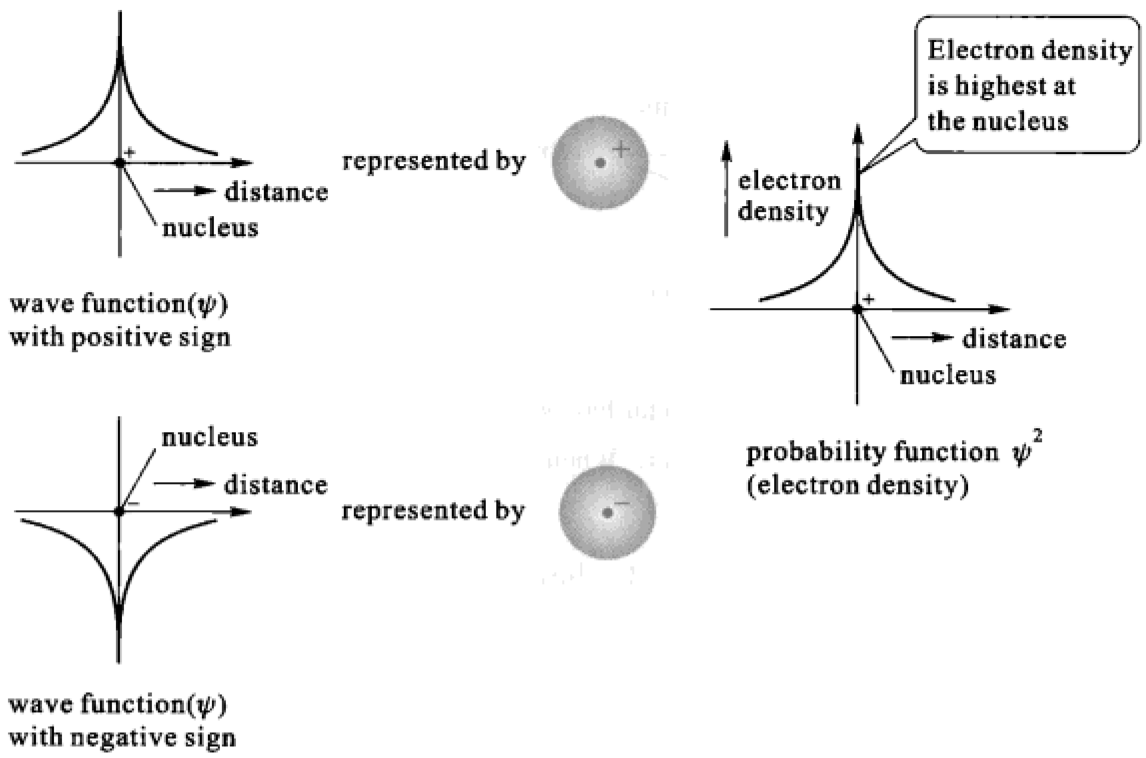


Figure 2−2 The 1*s* orbital. The 1*s* orbital is similar to the fundamental vibration of a guitar string. The wave function is instantaneously all positive or all negative. The square of the wave function gives the electron density. A circle with a nucleus is used to represent the spherically symmetrical *s* orbital.

If you gently place a finger at the center of a guitar string while plucking the string, your finger keeps the midpoint of the string from moving. The displacement (movement + or −) at the midpoint is always zero; this point is a **node**. The string now vibrates in two parts, with the two halves vibrating in opposite directions. We say that the two halves of the string are *out of phase*: When one is displaced upward, the other is displaced downward. Figure 2−3 shows this first *harmonic* of the guitar string.

The first harmonic of the guitar string resembles the 2*p* orbital (Figure 2−4). We have drawn the 2*p* orbital as two "lobes," separated by a node (a nodal plane). The two lobes of the *p* orbital are out of phase with each other. Whenever the wave function has a plus sign in one lobe, it has a minus sign in the other lobe.

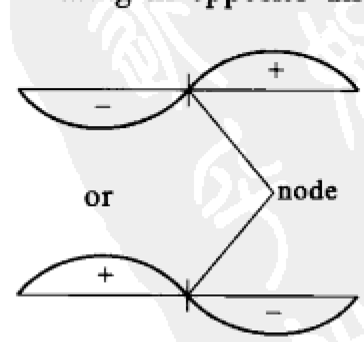


Figure 2−3 First harmonic of a guitar string. The two halves of the string are separated by a node, a point with zero displacement. The two halves vibrate out of phase with each other.

Linear Combination of Atomic Orbitals Atomic orbitals can combine and overlap to give more complex standing waves. We can add and subtract their wave functions to give the wave func-

tions of new orbitals. This process is called the **linear combination of atomic orbitals** (LCAO). The number of new orbitals generated always equals the number of orbitals we started with.

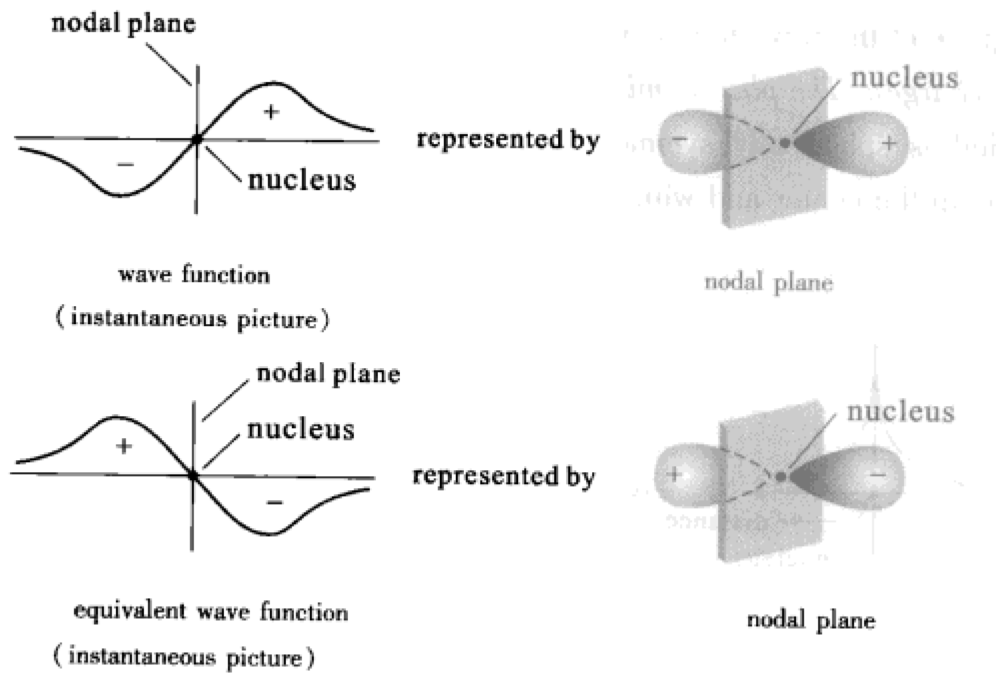


Figure 2–4 The 2*p* orbital. The 2*p* orbital has two lobes, separated by a nodal plane. The two lobes are out of phase with each other. When one has a plus sign, the other has a minus sign.

1. When orbitals on *different* atoms interact, they produce **molecular orbitals** (MOs) that lead to bonding (or antibonding).

2. When orbitals on the *same* atom interact, they give **hybrid atomic orbitals** that define the geometry of the bonds.

We begin by looking at how atomic orbitals on different atoms interact to give molecular orbitals. Then we consider how atomic orbitals on the same atom can interact to give hybrid atomic orbitals.

2–2 Molecular Orbitals

The stability of a covalent bond results from a large amount of electron density in the bonding region, the space between the two nuclei (Figure 2–5). In the bonding region, the electrons are close to both nuclei, resulting in a lowering of the overall energy. The bonding electrons also mask the positive charges of the nuclei, so the nuclei do not repel each other as much as they would otherwise.

There is always an optimum distance for the two bonded nuclei. If they are too far apart, their attraction for the bonding electrons is diminished. If they are too close together, their electrostatic repulsion pushes them apart. The internuclear distance where attraction and repulsion are balanced, which also gives the minimum energy (the strongest bond), is called the *bond length*.

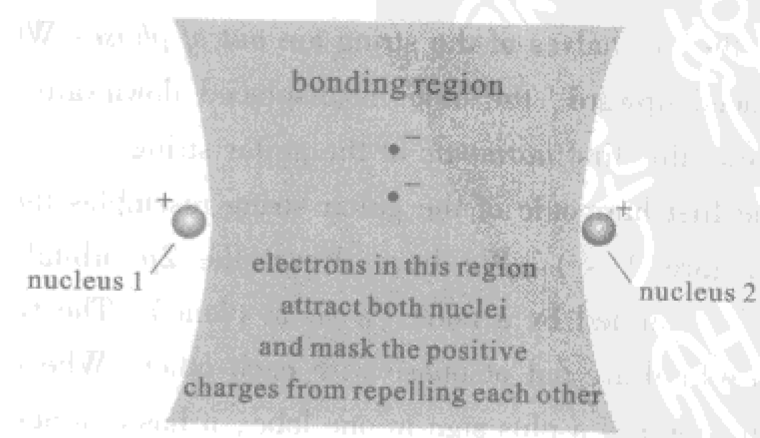


Figure 2–5 Electron density in a molecular orbital. A bonding molecular orbital places a large amount of electron density in the bonding region, the space between the two nuclei.

2-2A The Hydrogen Molecule; Sigma Bonding

The hydrogen molecule is the simplest example of covalent bonding. As two hydrogen atoms approach each other, their 1*s* wave functions can add *constructively* so that they reinforce each other, or *destructively* so that they cancel out where they overlap. Figure 2-6 shows how the wave functions interact constructively when they are in phase and have the same sign in the region between the nuclei. The wave functions reinforce each other and increase the electron density in this bonding region. The result is a **bonding molecular orbital** (bonding MO).

The bonding MO depicted in Figure 2-6 has most of its electron density centered *along the line connecting the nuclei*. This type of bond is called a *cylindrically symmetrical bond* or a **sigma bond** (σ bond). Sigma bonds are the most common bonds in organic compounds. All single bonds in organic compounds are sigma bonds, and every double or triple bond contains one sigma bond.

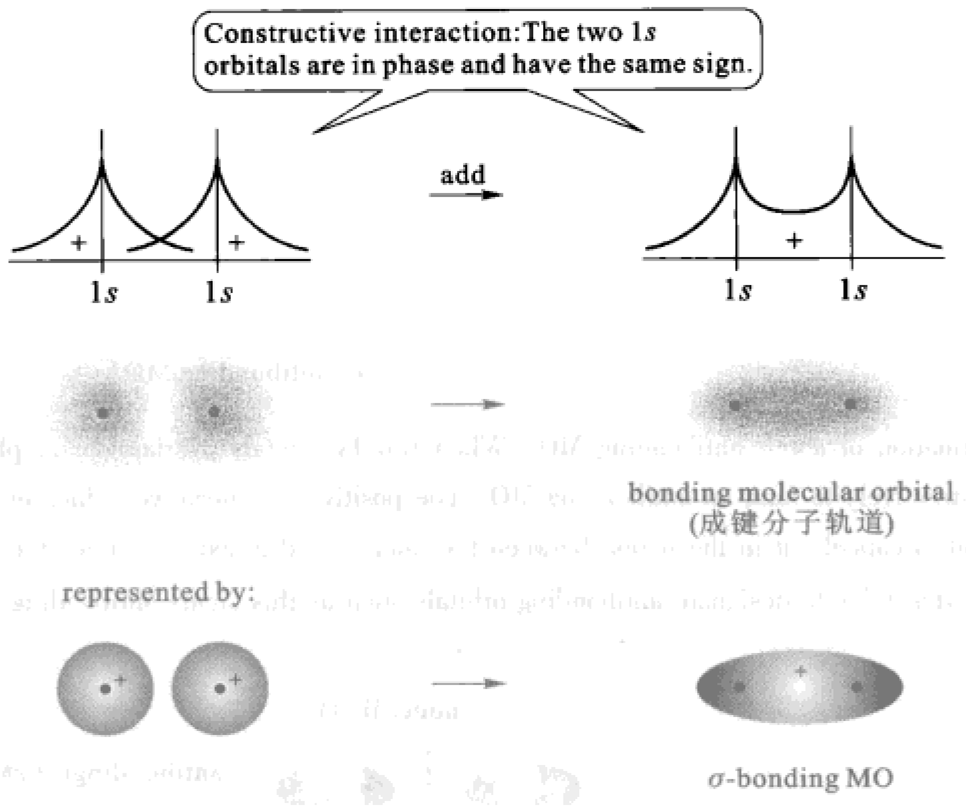


Figure 2-6 Formation of a σ-bonding MO. When the 1*s* orbitals of two hydrogen atoms overlap in phase, they interact constructively to form a bonding MO. The electron density in the bonding region (between the nuclei) is increased. The result is a cylindrically symmetrical bond, or sigma bond, designated σ.

When two hydrogen 1*s* orbitals overlap *out of phase* with each other, an **antibonding molecular orbital** results (Figure 2-7). The two 1*s* wave functions have opposite signs, so they tend to cancel out where they overlap. The result is a node (actually a nodal plane) separating the two atoms. The presence of a node separating the two nuclei usually indicates that the orbital is antibonding.

Figure 2-8 shows the relative energies of the atomic orbitals and the molecular orbitals of the H_2 system. When the 1*s* orbitals are in phase, the resulting molecular orbital is a sigma bonding MO, with lower energy than that of a 1*s* atomic orbital. When two 1*s* orbitals overlap out of phase, they form an antibonding (σ^*) orbital with higher energy than that of a 1*s* atomic orbital. The two electrons in the H_2 system are found with paired spins in the sigma bonding MO, giving a stable H_2 molecule. In stable molecules, the antibonding orbitals (such as σ^*) are usually vacant.

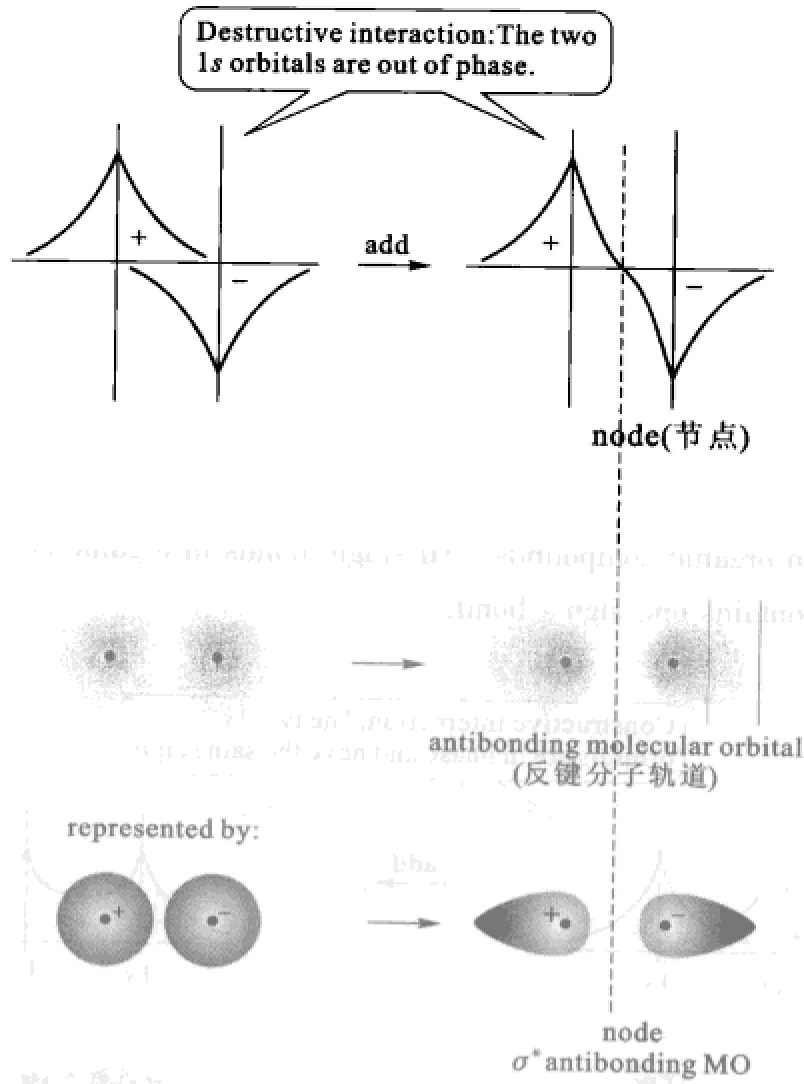


Figure 2−7 Formation of a σ^* antibonding MO. When two 1*s* orbitals overlap out of phase, they interact destructively to form an antibonding MO. The positive and negative values of the wave functions tend to cancel out in the region between the nuclei, and a node separates the nuclei. We use an asterisk (*) to designate antibonding orbitals such as this sigma antibonding orbital, σ^*.

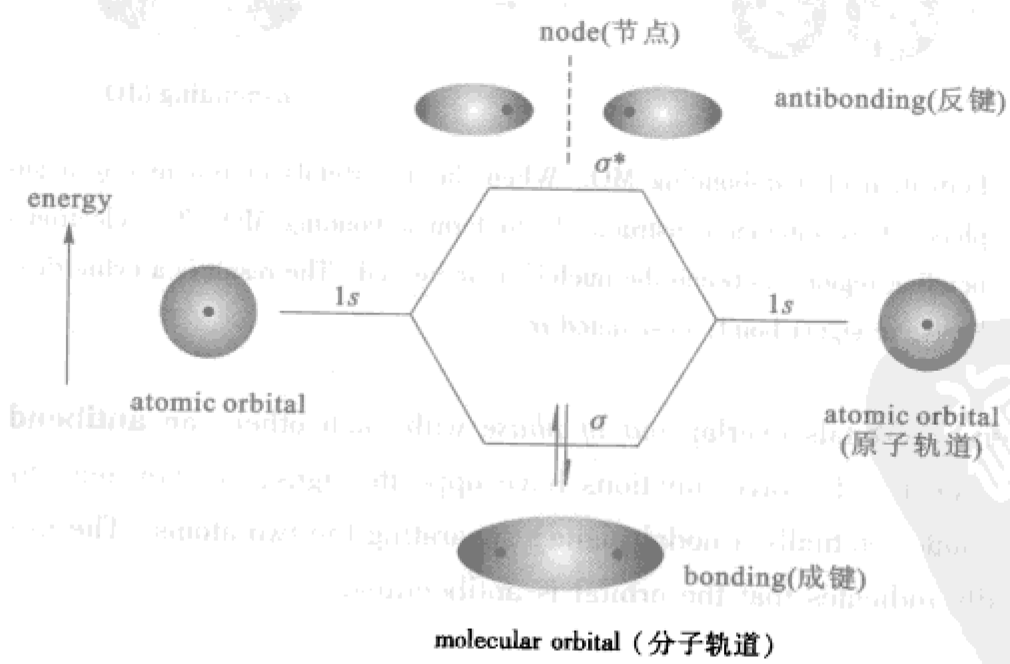
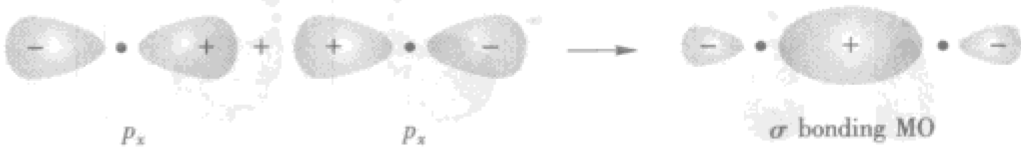


Figure 2−8 Relative energies of atomic and molecular orbitals. When the two hydrogen 1*s* orbitals overlap, a sigma bonding MO and a sigma antibonding MO result. The bonding MO is lower in energy than the atomic 1*s* orbital, and the antibonding orbital is higher in energy. Two electrons (represented by arrows) go into the bonding MO with opposite spins, forming a stable H_2 molecule. The antibonding orbital is vacant.

2-2B Sigma Overlap Involving *p* Orbitals

When two *p* orbitals overlap along the line between the nuclei, a bonding orbital and an antibonding orbital result. Once again, most of the electron density is centered along the line between the nuclei. This linear overlap is another type of sigma bonding MO. The constructive overlap of two *p* orbitals along the line joining the nuclei forms a σ bond represented as follows:

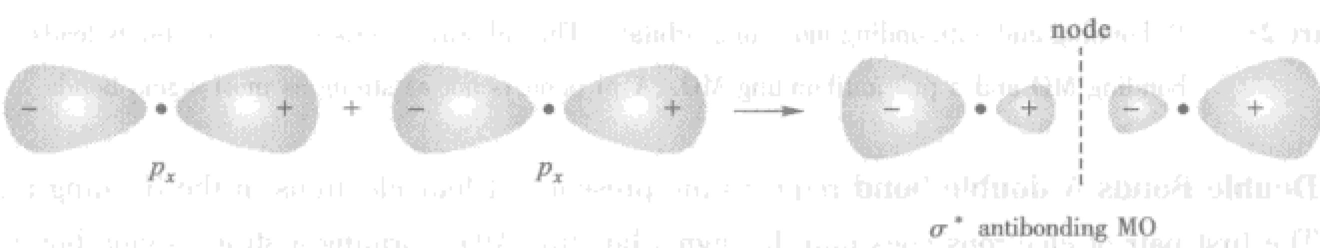


SOLVED PROBLEM 2-1

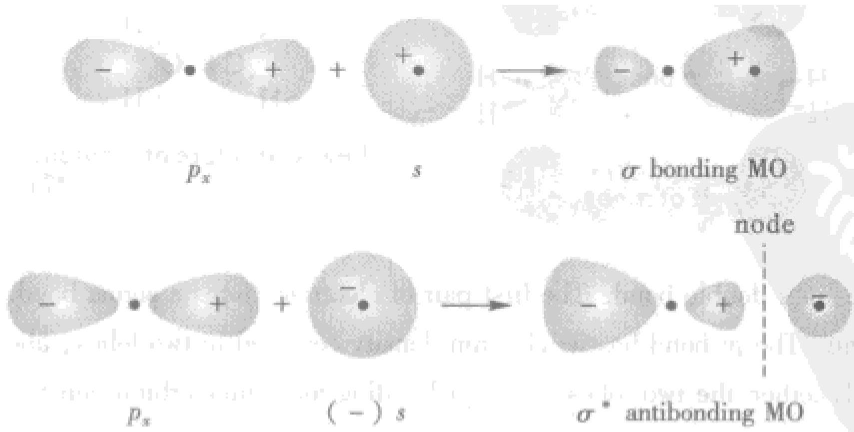
Draw the σ^* antibonding orbital that results from the destructive overlap of the two p_x orbitals just shown.

SOLUTION

This orbital results from the destructive overlap of lobes of the two *p* orbitals with opposite phases. If the signs are reversed on one of the orbitals, adding the two orbitals gives an antibonding orbital with a node separating the two nuclei:



Overlap of an *s* orbital with a *p* orbital also gives a bonding MO and an antibonding MO, as shown in the following illustration. Constructive overlap of the *s* orbital with the p_x orbital gives a sigma bonding MO with its electron density centered along the line between the nuclei. Destructive overlap gives a σ^* antibonding orbital with a node separating the nuclei.



2-3 Pi Bonding

A **pi bond** (**π bond**) results from overlap between two *p* orbitals oriented perpendicular to the line connecting the nuclei (Figure 2-9). These parallel orbitals overlap sideways, with most of the electron density centered

above and below the line connecting the nuclei. This overlap is parallel, not linear (as in a sigma bond), so a pi molecular orbital is *not* cylindrically symmetrical. Figure 2−9 shows a pi bonding MO and the corresponding pi* antibonding MO.

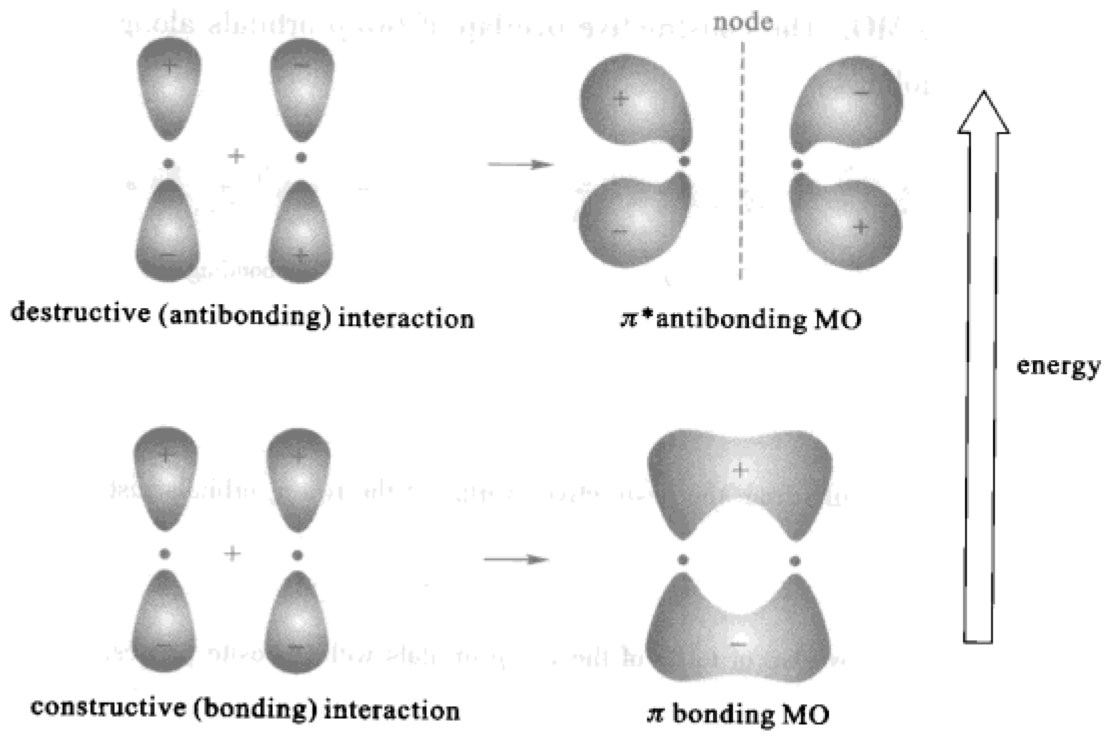


Figure 2−9 Pi bonding and antibonding molecular orbitals. The sideways overlap of two *p* orbitals leads to a pi bonding MO and a pi* antibonding MO. A pi bond is not as strong as most sigma bonds.

Single and Double Bonds A **double bond** requires the presence of four electrons in the bonding region between the nuclei. The first pair of electrons goes into the sigma bonding MO, forming a strong sigma bond. The second pair of electrons cannot go into the same orbital or the same space. It goes into a pi bonding MO, with its electron density centered above and below the sigma bond.

The combination of a sigma bond and a pi bond is the normal structure of a double bond. Figure 2−10 shows the structure of ethylene, an organic molecule containing a carbon-carbon double bond.

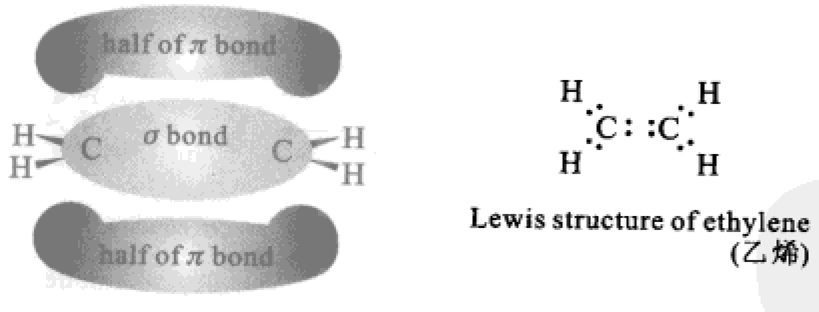


Figure 2−10 Structure of a double bond. The first pair of electrons forms a sigma bond. The second pair forms a pi bond. The pi bond has its electron density centered in two lobes, above and below the sigma bond. Together, the two lobes of the pi bonding molecular orbital constitute one bond.

Thus far, we have discussed only bonds involving overlap of simple *s* and *p* atomic orbitals. Although these simple bonds are occasionally seen in organic compounds, they are not as common as bonds formed using **hybrid atomic orbitals.** Hybrid atomic orbitals result from the mixing of orbitals on the *same* atom. The geometry of these hybrid orbitals helps us to account for the actual structures and bond angles observed in organic compounds.

2-4 Hybridization and Molecular Shapes

If we predict the bond angles of organic molecules using just the simple *s* and *p* orbitals, we expect bond angles of about 90°. The *s* orbitals are nondirectional (see Figure 1-3), and the *p* orbitals are oriented at 90° to one another. Experimental evidence shows, however, that bond angles in organic compounds are usually close to 109°, 120°, or 180° (Figure 2-11). A common way of accounting for these bond angles is the **valence-shell electron-pair repulsion theory (VSEPR theory)**: Electron pairs repel each other, and the bonds and lone pairs around a central atom generally are separated by the largest possible angles. An angle of 109.5° is the largest possible separation for four pairs of electrons; 120° is the largest separation for three pairs; and 180° is the largest separation for two pairs. All the structures in Figure 2-11 have bond angles that separate their bonds about as far apart as possible.

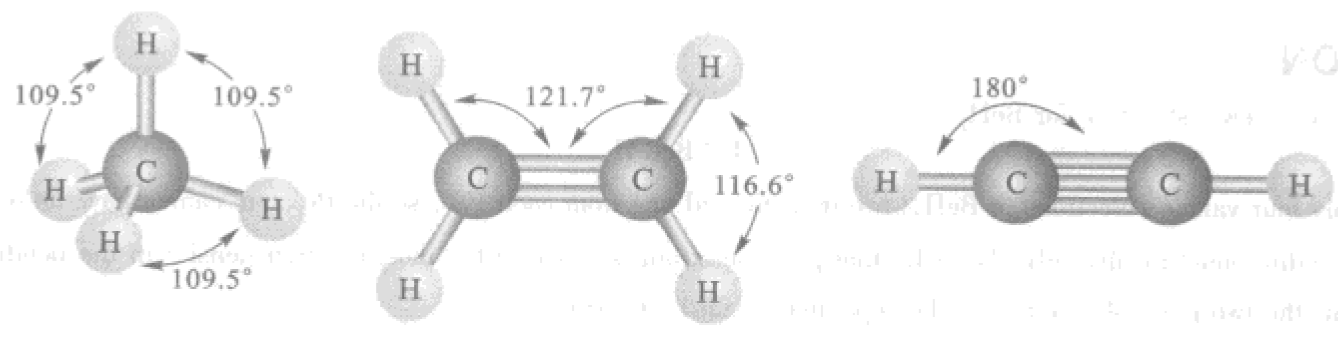


Figure 2-11 Common bond angles. Bond angles in organic compounds are usually close to 109°, 120°, or 180°.

The shapes of these molecules cannot result from bonding between simple *s* and *p* atomic orbitals. Although these orbitals have the lowest energies for isolated atoms in space, they are not the best for forming bonds. To explain the shapes of common organic molecules, we assume that the *s* and *p* orbitals combine to form hybrid atomic orbitals that separate the electron pairs more widely in space and place more electron density in the bonding region between the nuclei.

2-4A *sp* Hybrid Orbitals

Orbitals can interact to form new orbitals. We have used this principle to form molecular orbitals by adding and subtracting atomic orbitals on *different* atoms, but we can also add and subtract orbitals on the *same* atom. Consider the result when we combine a *p* orbital and an *s* orbital on the same atom (Figure 2-12).

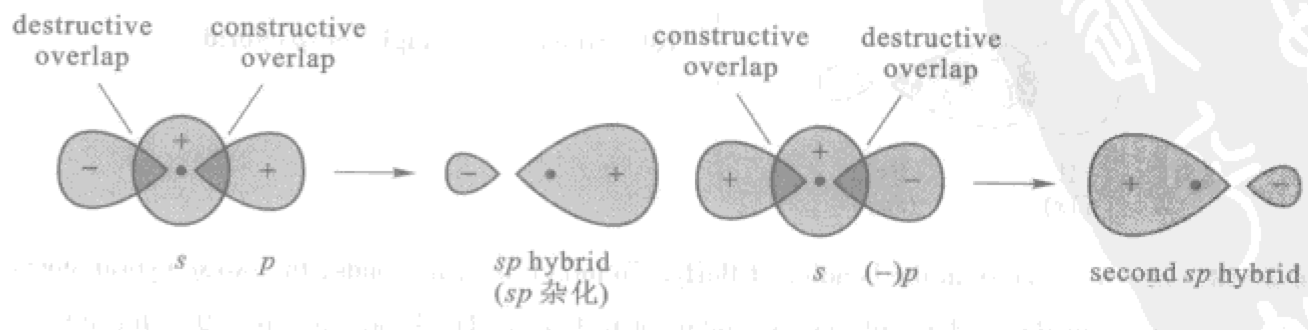


Figure 2-12 Formation of a pair of *sp* hybrid atomic orbitals. Addition of an *s* orbital to a *p* orbital gives an *sp* hybrid atomic orbital, with most of its electron density on one side of the mucleus. Adding the *p* orbital with opposite phase gives the other *sp* hybrid atomic orbital, with most of its electron density on the opposite side of the nucleus from the first hybrid.

The resulting orbital is called an ***sp* hybrid orbital**. Its electron density is concentrated toward one side of the atom. We started with two orbitals (*s* and *p*), so we must finish with two *sp* hybrid orbitals. The second *sp* hybrid orbital results if we add the *p* orbital with the opposite phase (Figure 2−12).

The result of this hybridization is a pair of directional *sp* hybrid orbitals pointed in opposite directions. These hybridized orbitals provide enhanced electron density in the bonding region for a sigma bond toward the left of the atom and for another sigma bond toward the right. In addition, these hybrid orbitals give a bond angle of 180°, separating the bonding electrons as much as possible. In general, *sp* hybridization results in this **linear** bonding arrangement.

SOLVED PROBLEM 2−2

Draw the Lewis structure for beryllium hydride, BeH_2. Draw the orbitals that overlap in the bonding of BeH_2, and label the hybridization of each orbital. Predict the H—Be—H bond angle.

SOLUTION

First, we draw a Lewis structure for BeH_2.

H : Be : H

There are only four valence electrons in BeH_2 (two from Be and one from each H) , so the Be atom cannot have an octet of electrons. The bonding must involve orbitals on Be that give the strongest bonds (the most electron density in the bonding region) and also allow the two pairs of electrons to be separated as far as possible.

Hybrid orbitals concentrate the electron density in the bonding region, and *sp* hybrids give 180° separation for two pairs of electrons. Hydrogen cannot use hybridized orbitals, since the closest available *p* orbitals are the 2*p*'s, and they are much higher in energy than the 1*s*. The bonding in BeH_2 results from overlap of *sp* hybrid orbitals on Be with the 1*s* orbitals on hydrogen. Figure 2−13 shows how this occurs.

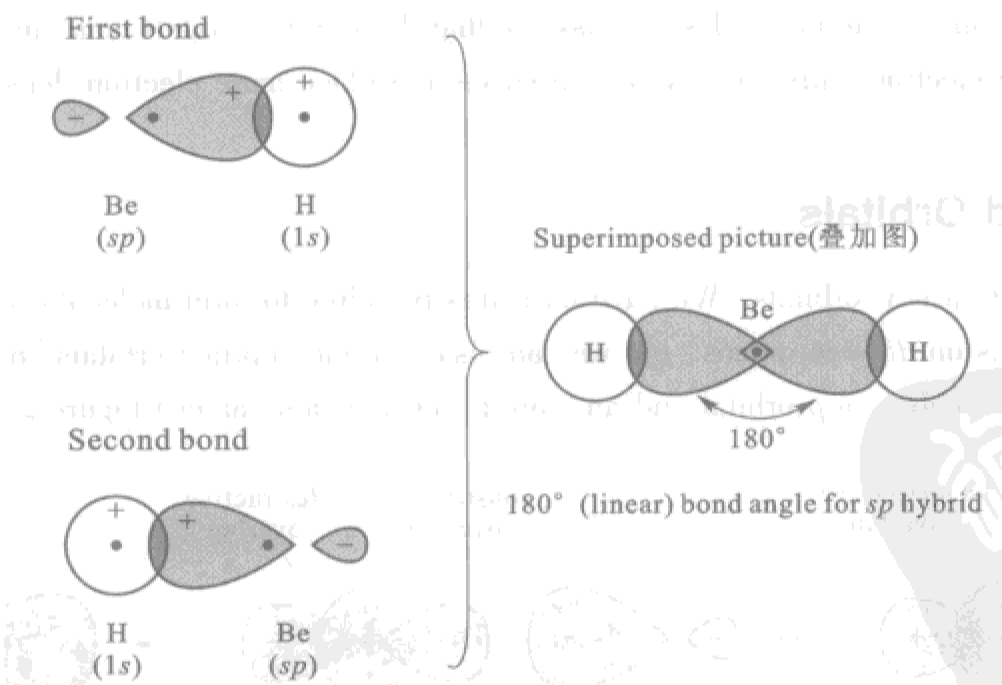


Figure 2−13 Linear geometry in the bonding of BeH_2. To form two sigma bonds, the two *sp* hybrid atomic orbitals on Be overlap with the 1*s* orbitals of hydrogen. The bond angle is 180° (linear).

2−4B sp^2 Hybrid Orbitals

To orient three bonds as far apart as possible, bond angles of 120° are required. When an *s* orbital combines with

two p orbitals, the resulting three hybrid orbitals are oriented at 120° angles to each other (Figure 2-14). These orbitals are called ***sp*² hybrid orbitals** because they are composed of one s and two p orbitals. The 120° arrangement is called **trigonal** geometry, in contrast to the linear geometry associated with sp hybrid orbitals. There remains an unhybridized p orbital (p_z) perpendicular to the plane of the three sp^2 hybrid orbitals.

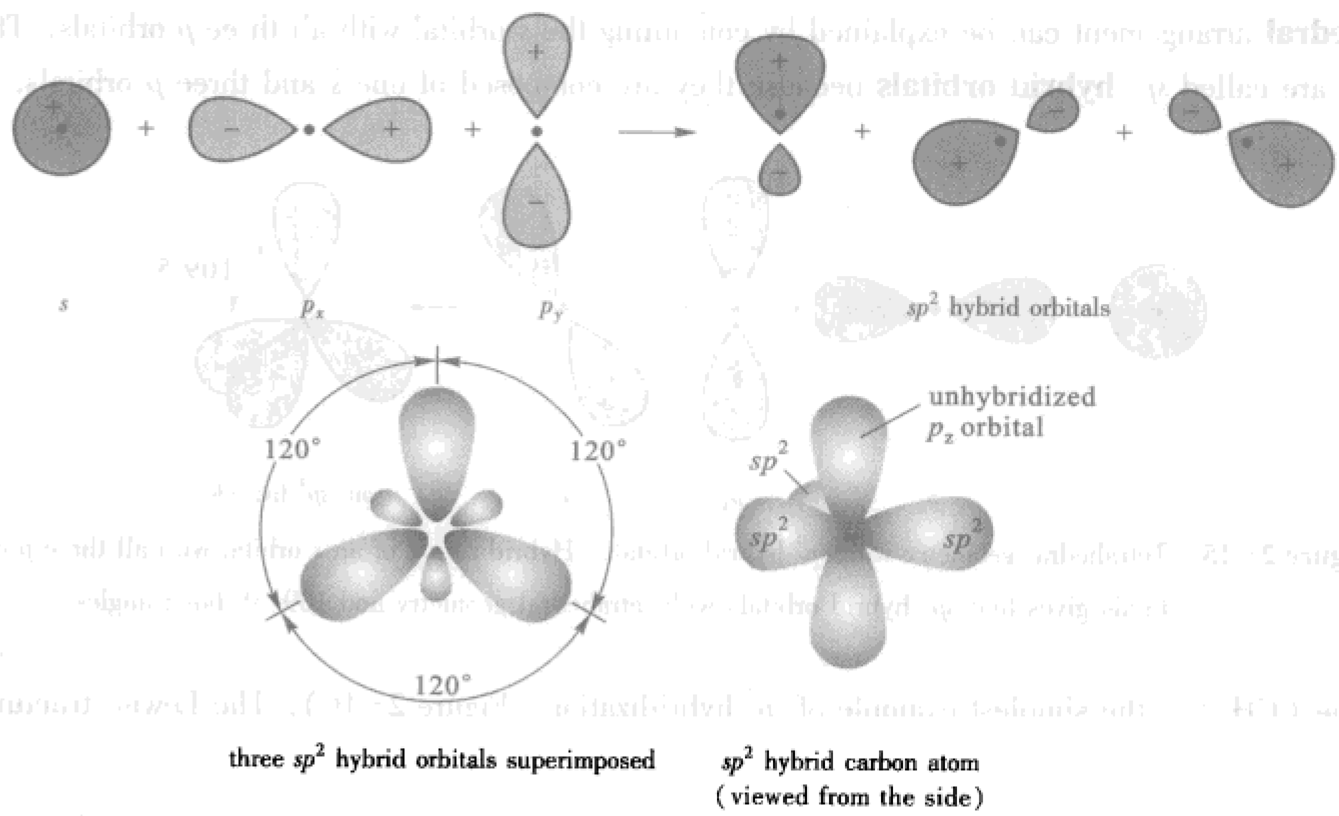


Figure 2-14 Trigonal geometry with sp^2 hybrid orbitals. Hybridization of an s orbital with two p orbitals gives a set of three sp^2 hybrid orbitals. The bond angles associated with this trigonal structure are about 120°. The remaining p orbital is perpendicular to the plane of the three hybrid orbitals.

SOLVED PROBLEM 2-3

Borane (BH_3) is not stable under normal conditions, but it has been detected at low pressure.

(a) Draw the Lewis structure for borane.

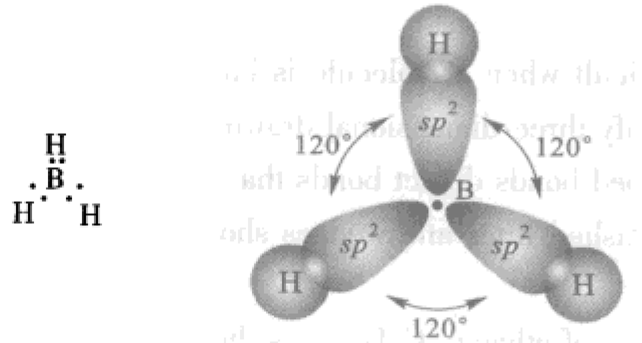
(b) Draw a diagram of the bonding in this molecule, and label the hybridization of each orbital.

(c) Predict the H—B—H bond angle.

SOLUTION

There are only six valence electrons in borane. Boron has a single bond to each of the three hydrogen atoms.

The best bonding orbitals are those that provide the greatest electron density in the bonding region while keeping the three pairs of bonding electrons as far apart as possible. Hybridization of an s orbital with two p orbitals gives three sp^2 hybrid orbitals directed 120° apart. Overlap of these orbitals with the hydrogen 1s orbitals gives a planar, trigonal molecule. (Note that the small back lobes of the hybrid orbitals have been omitted.)



2-4C sp^3 Hybrid Orbitals

Many organic compounds contain carbon atoms that are bonded to four other atoms. When four bonds are oriented as far apart as possible, they form a regular tetrahedron (109.5° bond angles), as pictured in Figure 2-15. This **tetrahedral** arrangement can be explained by combining the *s* orbital with all three *p* orbitals. The resulting four orbitals are called sp^3 **hybrid orbitals** because they are composed of one *s* and three *p* orbitals.

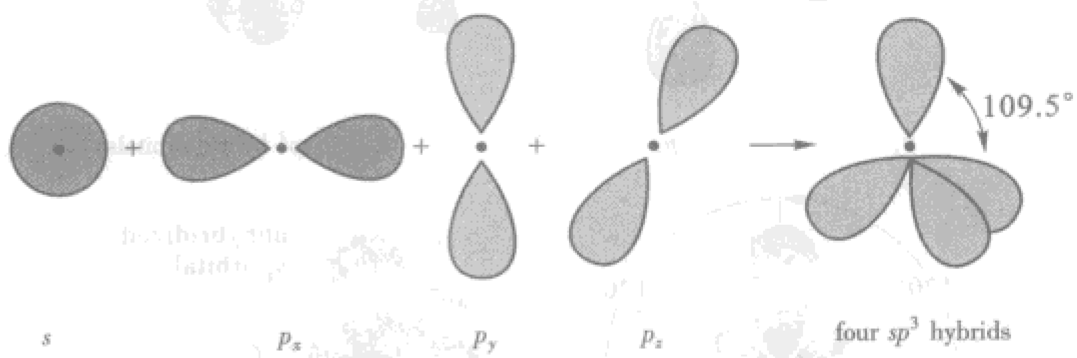


Figure 2-15 Tetrahedral geometry with sp^3 hybrid orbitals. Hybridization of an *s* orbital with all three *p* orbitals gives four sp^3 hybrid orbitals with tetrahedral geometry and 109.5° bond angles.

Methane (CH_4) is the simplest example of sp^3 hybridization (Figure 2-16). The Lewis structure for methane has eight valence electrons (four from carbon and one from each hydrogen), corresponding to four C—H single bonds. Tetrahedral geometry separates these bonds by the largest possible angle, 109.5°.

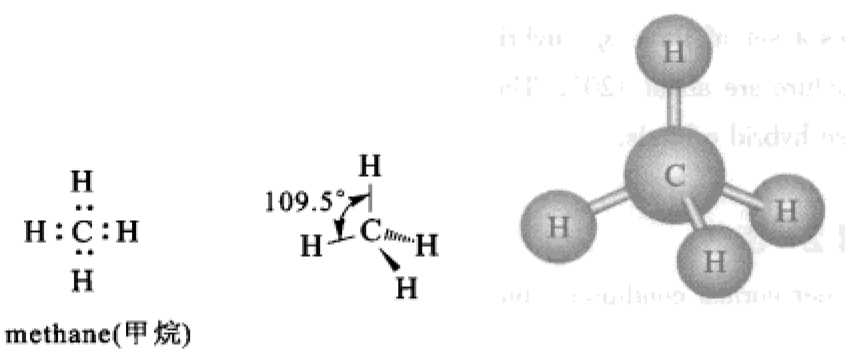


Figure 2-16 Several views of methane. Methane has tetrahedral geometry, using four sp^3 hybrid orbitals to form sigma bonds to the four hydrogen atoms.

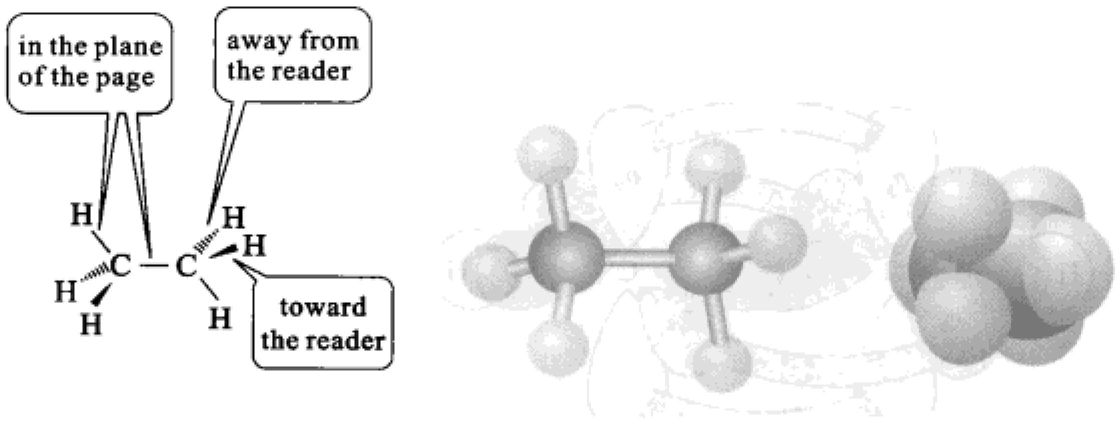
2-5 Drawing Three-Dimensional Molecules

Figures 2-15 and 2-16 were more difficult to draw than the earlier figures because they depict three-dimensional objects on a two-dimensional piece of paper. The p_z orbital should look like it points in and out of the page, and the tetrahedron should look three-dimensional. These drawings use perspective and the viewer's imagination to add the third dimension.

The use of perspective is difficult when a molecule is large and complicated. Organic chemists have developed a shorthand notation to simplify three-dimensional drawings. Dashed lines indicate bonds that go backward, away from the reader. Wedge-shaped bonds depict bonds that come forward, toward the reader. Straight lines are bonds in the plane of the page. Dashed lines and wedges show perspective in the second drawing of methane in Figure 2-16.

The three-dimensional structure of ethane, C_2H_6, has the shape of two tetrahedra joined together. Each carbon atom is sp^3 hybridized, with four sigma bonds formed by the four sp^3 hybrid orbitals. All the bond angles are

close to 109.5° (Figure 2-17).



ethane (乙烷) ethane ethane

Figure 2-17 Several views of ethane.

2-6 General Rules of Hybridization and Geometry

At this point, we can consider some general rules for determining the hybridization of orbitals and the bond angles of atoms in organic molecules. After stating these rules, we solve some problems to show how the rules are used.

Rule 1: Both sigma bonding electrons and lone pairs can occupy hybrid orbitals. The number of hybrid orbitals on an atom is computed by adding the number of sigma bonds and the number of lone pairs of electrons on that atom.

Because the first bond to another atom is always a sigma bond, the number of hybrid orbitals may be computed by adding the number of lone pairs to the number of atoms bonded to the central atom.

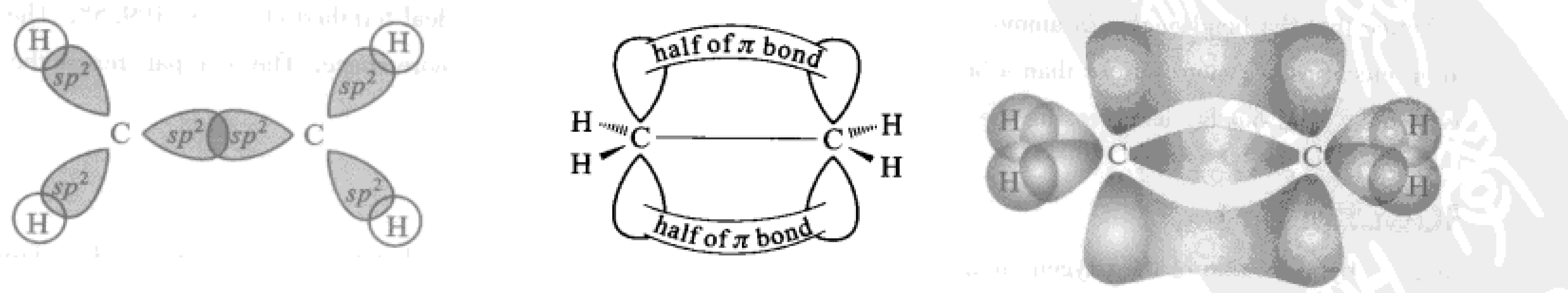
Rule 2: Use the hybridization and geometry that give the widest possible separation of the calculated number of bonds and lone pairs.

Summary of Hybridization and Geometry

Hybrid Orbitals	Hybridization	Geometry	Approximate Bond Angles
2	$s + p = sp$	linear	180°
3	$s + p + p = sp^2$	trigonal	120°
4	$s + p + p + p = sp^3$	tetrahedral	109.5°

The number of hybrid orbitals obtained equals the number of atomic orbitals combined. Lone pairs of electrons take up more space than bonding pairs of electrons, thus they compress the bond angles.

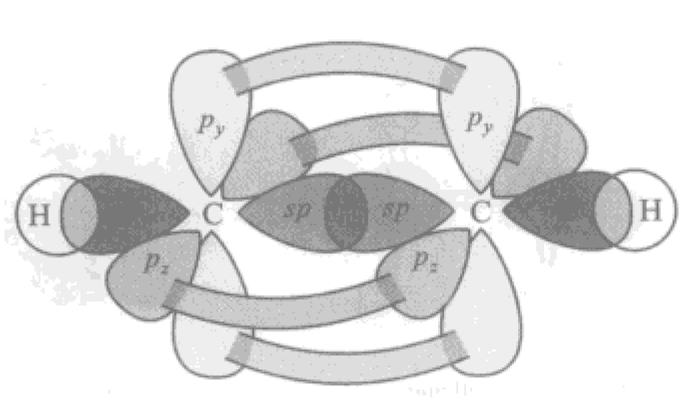
Rule 3: If two or three pairs of electrons form a multiple bond between two atoms, the first bond is a sigma bond formed by a hybrid orbital. The second bond is a pi bond, consisting of two lobes above and below the sig-



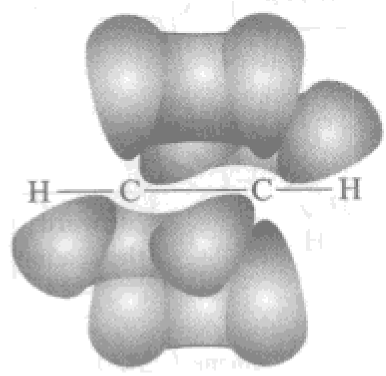
σ bond framework (σ 键) (viewed from above the plane) π bond (π 键) (viewed from alongside the plane) ethylene (乙烯)

Figure 2-18 Planar geometry of ethylene. The carbon atoms in ethylene are sp^2 hybridized, with trigonal bond angles of about 120°. All the carbon and hydrogen atoms lie in the same plane.

ma bond, formed by two *p* orbitals (see Figure 2−18). The third bond of a triple bond is another pi bond, perpendicular to the first pi bond (Figure 2−19).



acetylene (乙炔)



acetylene

Figure 2−19 Linear geometry of acetylene. The carbon atoms in acetylene are *sp* hybridized, with linear (180°) bond angles. The triple bond contains one sigma bond and two perpendicular pi bonds.

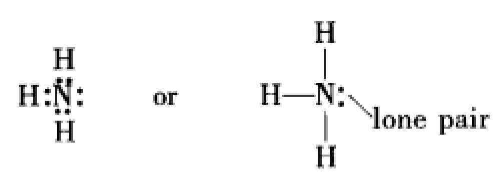
Solved Problems 2−4 through 2−7 show how to use these rules to predict the hybridization and bond angles in organic compounds.

SOLVED PROBLEM 2−4

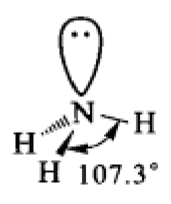
Predict the hybridization of the nitrogen atom in ammonia, NH_3. Draw a picture of the three-dimensional structure of ammonia, and predict the bond angles.

SOLUTION

The hybridization depends on the number of sigma bonds plus lone pairs. A Lewis structure provides this information.



In this structure, there are three sigma bonds and one pair of nonbonding electrons. Four hybrid orbitals are required, implying sp^3 hybridization and tetrahedral geometry around the nitrogen atom, with bond angles of about 109.5°. The resulting structure is much like that of methane, except that one of the sp^3 hybrid orbitals is occupied by a lone pair of electrons.



Notice that the bond angles in ammonia (107.3°) are slightly smaller than the ideal tetrahedral angle, 109.5°. The nonbonding electrons are more diffuse than a bonding pair of electrons, and they take up more space. The lone pair repels the electrons in the N—H bonds, compressing the bond angle.

PROBLEM 2−1

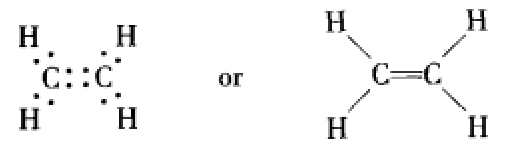
Predict the hybridization of the oxygen atom in water, H_2O. Draw a picture of its three-dimensional structure, and explain why its bond angle is 104.5°.

SOLVED PROBLEM 2−5

Predict the hybridization, geometry, and bond angles for ethylene (C_2H_4).

SOLUTION

The Lewis structure of ethylene is



Each carbon atom has an octet, and there is a double bond between the carbon atoms. Each carbon is bonded to three other atoms (three sigma bonds), and there are no lone pairs. The carbon atoms are sp^2 hybridized, and the bond angles are trigonal: about 120°. The double bond is composed of a sigma bond formed by overlap of two sp^2 hybridized orbitals, plus a pi bond formed by overlap of the unhybridized p orbitals remaining on the carbon atoms. Because the pi bond requires parallel alignment of its two p orbitals, the ethylene molecule must be planar (Figure 2-18).

PROBLEM 2-2

Predict the hybridization, geometry, and bond angles for the central atoms in

(a) 2-butene, $CH_3CH{=}CHCH_3$

(b) $CH_2{=}NCH_3$

SOLVED PROBLEM 2-6

Predict the hybridization, geometry, and bond angles for the carbon atoms in acetylene, C_2H_2.

SOLUTION

The Lewis structure of acetylene is

$$H{:}C{:::}C{:}H \quad \text{or} \quad H{-}C{\equiv}C{-}H$$

Both carbon atoms have octets, but each carbon is bonded to just two other atoms, requiring two sigma bonds. There are no lone pairs. Each carbon atom is sp hybridized and linear (180° bond angles). The sp hybrid orbitals are generated from the s orbital and the p_x orbital (the p orbital directed along the line joining the nuclei). The p_y orbitals and the p_z orbitals are unhybridized.

The **triple bond** is composed of one sigma bond, formed by overlap of sp hybrid orbitals, plus two pi bonds. One pi bond results from overlap of the two p_y orbitals and another from overlap of the two p_z orbitals (Figure 2-19).

PROBLEM 2-3

Predict the hybridization, geometry, and bond angles for the carbon and nitrogen atoms in acetonitrile ($CH_3{-}C{\equiv}N{:}$).

PROBLEM 2-4

1. Draw a Lewis structure for each of the following compounds.
2. Label the hybridization, geometry, and bond angles around each atom other than hydrogen.
3. Draw a three-dimensional representation (using wedges and dashed lines) of the structure.

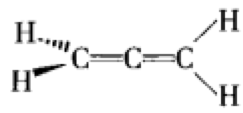
(a) CO_2 (b) $CH_3{-}O{-}CH_3$ (c) $(CH_3)_3N$

(d) HCOOH (e) HCN (f) $CH_3CH{=}CH_2$

(g) ozone (O_3), bonded OOO

PROBLEM 2-5

Allene, $CH_2{=}C{=}CH_2$, has the structure shown below. Explain how the bonding in allene requires the two $=CH_2$ groups at its ends to be at right angles to each other.



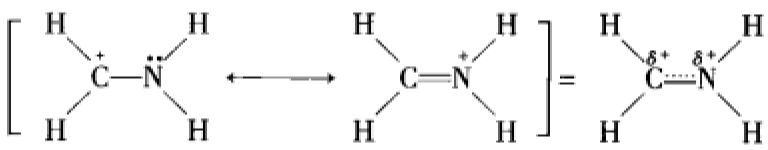
allene (丙二烯)

SOLVED PROBLEM 2-7

In Chapter 1, we considered the electronic structure of $[CH_2NH_2]^+$. Predict its hybridization, geometry, and bond angles.

SOLUTION

This is a tricky question. This ion has two important resonance forms:

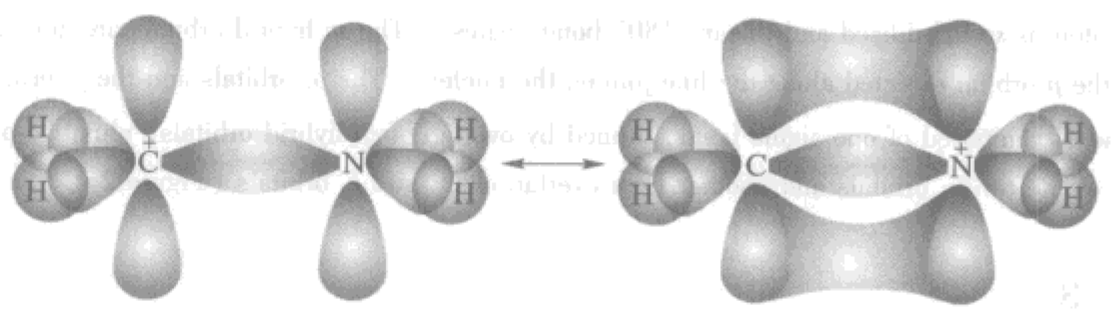


resonance forms (共振式) combined representation

When resonance is involved, different resonance forms may suggest different hybridization and bond angles. Only electrons can be delocalized, however. The molecule can have only one set of bond angles, which must be compatible with all the important resonance forms. Looking at either resonance form for $[CH_2NH_2]^+$, we would predict sp^2 hybridization (120° bond angles) for the carbon atom; however, the first resonance form suggests sp^3 hybridization for nitrogen (109° bond angles), and the second suggests sp^2 hybridization (120° bond angles). Which is correct?

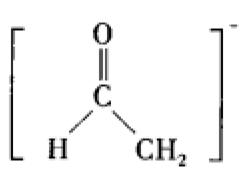
Experiments show that the bond angles on both carbon and nitrogen are about 120°, implying sp^2 hybridization. Nitrogen cannot be sp^3 hybridized because there must be an unhybridized p orbital available to form the pi bond in the second resonance form. In the first resonance form we picture the lone pair residing in this unhybridized p orbital.

In general, resonance-stabilized structures have bond angles appropriate for the largest number of pi bonds needed at each atom; that is, with unhybridized p orbitals available for all the pi bonds shown in any important resonance form.



PROBLEM 2-6

1. Draw the important resonance forms for each compound.
2. Label the hybridization and bond angles around each atom other than hydrogen.
3. Use a three-dimensional drawing to show where the electrons are pictured to be in each resonance form.

(a) $[H_2COH]^+$ (b)  (c) $[H_2CCN]^-$ (d) $B(OH)_3$

2-7 Bond Rotation

Some bonds rotate easily, but others do not. When we look at a structure, we must recognize which bonds rotate and which do not. If a bond rotates easily, each molecule can rotate through the different angular arrangements of

atoms. If a bond cannot rotate, however, different angular arrangements may be distinct compounds (isomers) with different properties.

2-7A Rotation of Single Bonds

In ethane (CH_3—CH_3), both carbon atoms are sp^3 hybridized and tetrahedral. Ethane looks like two methane molecules that have each had a hydrogen plucked off (to form a methyl group) and are joined by overlap of their sp^3 orbitals (Figure 2-20).

We can draw many structures for ethane, differing only in how one methyl group is twisted in relation to the other one. Such structures, differing only in rotations about a single bond, are called *conformations*. Two of the infinite number of conformations of ethane are shown in Figure 2-20. Construct a molecular model of ethane, and twist the model into these two conformations.

Which of these structures for ethane is the "right" one? Are the two methyl groups lined up so that their C—H bonds are parallel (*eclipsed*), or are they *staggered*, as in the drawing on the right? The answer is that both structures, and all the possible structures in between, are correct structures for ethane, and a real ethane molecule rotates through all these conformations. The two carbon atoms are bonded by overlap of their sp^3 orbitals to form a sigma bond along the line between the carbons. The magnitude of this sp^3-sp^3 overlap remains nearly the same during rotation because the sigma bond is cylindrically symmetrical about the line joining the carbon nuclei. No matter how you turn one of the methyl groups, its sp^3 orbital still overlaps with the sp^3 orbital of the other carbon atom.

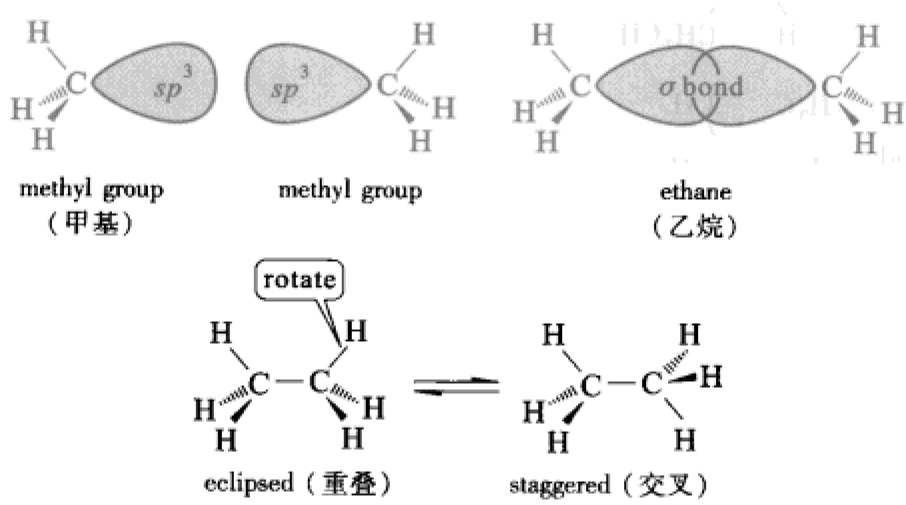
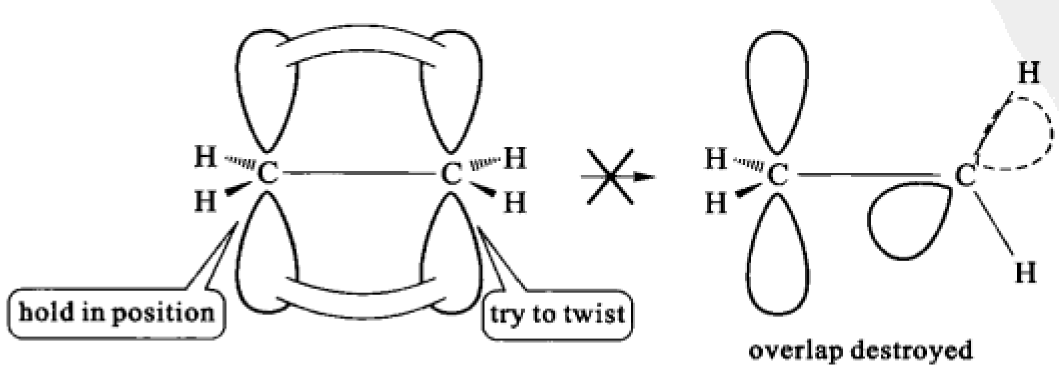


Figure 2-20 Rotation of single bonds. Ethane is composed of two methyl groups bonded by overlap of their sp^3 hybrid orbitals. These methyl groups may rotate with respect to each other.

2-7B Rigidity of Double Bonds

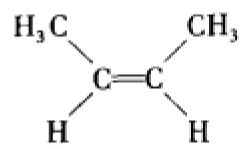
Not all bonds allow free rotation; ethylene, for example is quite rigid. In ethylene, the double bond between the two CH_2 groups consists of a sigma bond and a pi bond. When we twist one of the two CH_2 groups, the sigma bond is unaffected but the pi bond loses its overlap. The two p orbitals cannot overlap when the two ends of the molecule are at right angles, and the pi bond is effectively broken.



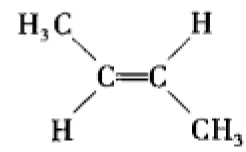
We can make the following generalization:

Rotation about single bonds is allowed, but double bonds are rigid and cannot be twisted.

Because double bonds are rigid, we can separate and isolate compounds that differ only in how their substituents are arranged on a double bond. For example, the double bond in 2-butene (CH_3—CH=CH—CH_3) prevents the two ends of the molecule from rotating. Two different compounds are possible, and they have different physical properties:



cis-2-butene (顺-2-丁烯)
bp = 3.7 ℃

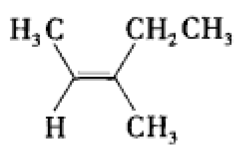
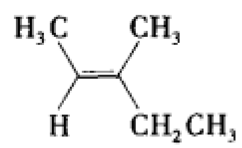


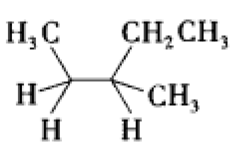
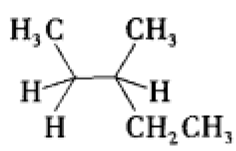
trans-2-butene (反-2-丁烯)
bp = 0.9 ℃

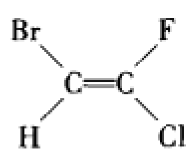
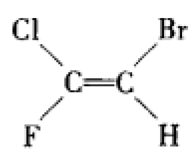
The molecule with the methyl groups on the same side of the double bond is called *cis*-2-butene, and the one with the methyl groups on opposite sides is called *trans*-2-butene. These kinds of molecules are discussed further in Section 2-8B.

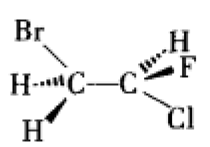
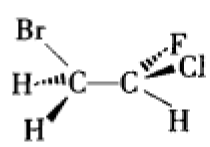
PROBLEM 2-7

For each pair of structures, determine whether they represent different compounds or a single compound.

(a)  and 

(b)  and 

(c)  and 

(d)  and 

PROBLEM 2-8

Two compounds with the formula CH_3—CH=N—CH_3 are known.

(a) Draw a Lewis structure for this molecule, and label the hybridization of each carbon and nitrogen atom.

(b) What two compounds have this formula?

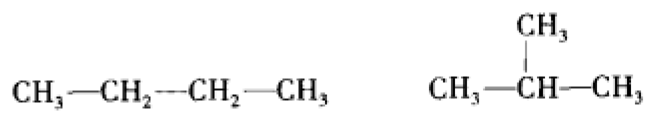
(c) Explain why there is only one compound known with the formula $(CH_3)_2CNCH_3$.

2-8 Isomerism

Isomers are different compounds with the same molecular formula. There are several types of isomerism in organic compounds, and we will cover them in detail in Chapter 6 (Stereochemistry). For now, we need to recognize the two large classes of isomers: constitutional isomers and stereoisomers.

2-8A Constitutional Isomerism

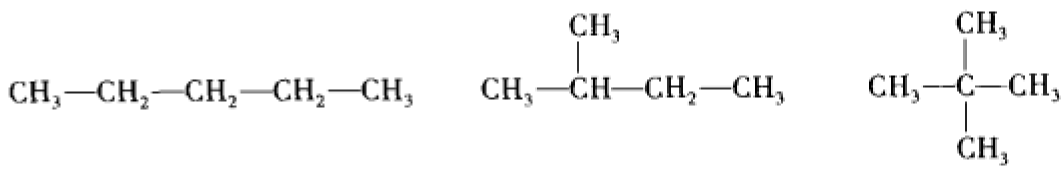
Constitutional isomers (or **structural isomers**) are isomers that differ in their bonding sequence; that is, their atoms are connected differently. Let's use butane as an example. If you were asked to draw a structural formula for C_4H_{10}, either of the following structures would be correct:



n-butane (正丁烷) isobutane (异丁烷)

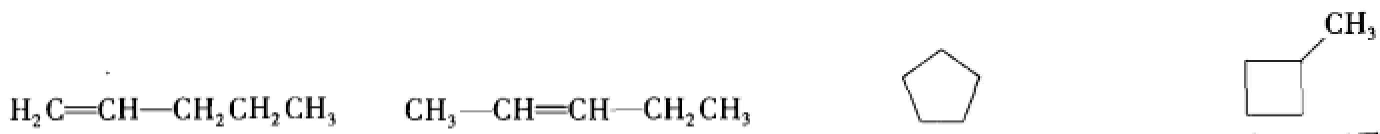
These two compounds are isomers because they have the same molecular formula. They are constitutional isomers because their atoms are connected differently. The first compound (*n*-butane for "normal" butane) has its carbon atoms in a straight chain four carbons long. The second compound ("isobutane" for "an isomer of butane") has a branched structure with a longest chain of three carbon atoms and a methyl side chain.

.There are three constitutional isomers of pentane (C_5H_{12}), whose common names are *n*-pentane, isopentane, and neopentane. The number of isomers increases rapidly as the number of carbon atoms increases.



n-pentane (正戊烷) isopentane (异戊烷) neopentane (新戊烷)

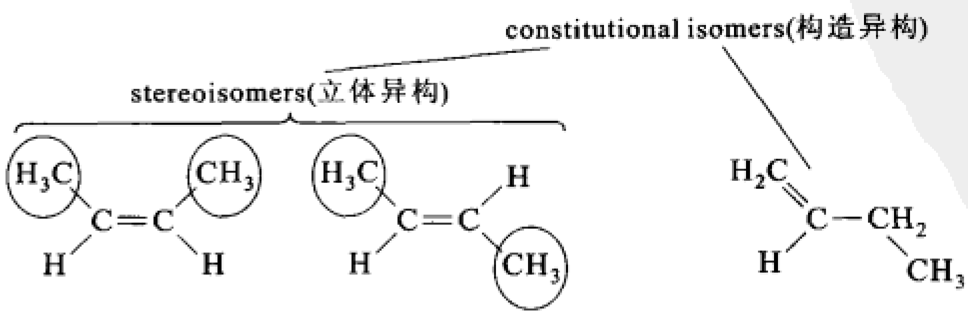
Constitutional isomers may differ in ways other than the branching of their carbon chain. They may differ in the position of a double bond or other group or by having a ring or some other feature. Notice how the following constitutional isomers all differ by the ways in which atoms are bonded to other atoms. (Check the number of hydrogens bonded to each carbon.) These compounds are not isomers of the pentanes just shown, however, because these have a different molecular formula (C_5H_{10}).



1-pentene (1-戊烯) 2-pentene (2-戊烯) cyclopentane (环戊烯) methylcyclobutane (甲基环丁烷)

2-8B Stereoisomers

Stereoisomers are isomers that differ only in how their atoms are oriented in space. Their atoms are bonded in the same order, however. For example, *cis*-and *trans*-2-butene have the same connections of bonds, so they are not constitutional isomers. They are stereoisomers because they differ only in the spatial orientation of the groups attached to the double bond. The cis isomer has the two methyl groups on the same side of the double bond, and the trans isomer has them on opposite sides. In contrast, 1-butene is a constitutional isomer of *cis*-and *trans*-2-butene.

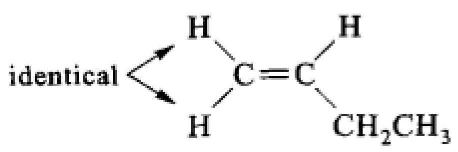


cis-2-butene (顺-2-丁烯) *trans*-2-butene 反-2-丁烯 1-butene (1-丁烯)

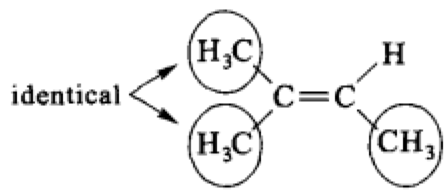
Cis and trans isomers are only one type of stereoisomerism. The study of the structure and chemistry of stereoisomers is called **stereochemistry**. We will encounter stereochemistry throughout our study of organic chemistry, and Chapter 6 is devoted entirely to this field.

Cis-trans isomers are also called **geometric isomers** because they differ in the geometry of the groups on a double bond. The cis isomer is always the one with similar groups on the same side of the double bond, and the trans isomer has similar groups on opposite sides of the double bond.

To have cis-trans isomerism, there must be two *different* groups on each end of the double bond. For example, 1-butene has two identical hydrogens on one end of the double bond. Reversing their positions does not give a different compound. Similarly, 2-methyl-2-butene has two identical methyl groups on one end of the double bond. Reversing the methyl groups does not give a different compound.



1-butene
no cis or trans

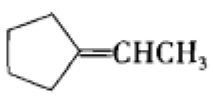


2-methyl-2-butene (2-甲基-2-丁烯)
no cis or trans

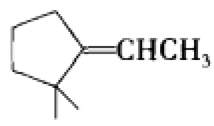
PROBLEM 2-9

Which of the following compounds show cis-trans isomerism? Draw the cis and trans isomers of those that do.

(a) CHF=CHF **(b)** $F_2C{=}CH_2$ **(c)** $CH_2{=}CH{-}CH_2{-}CH_3$

(d) 

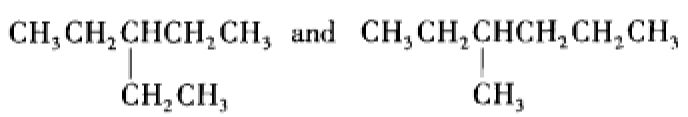
(e)

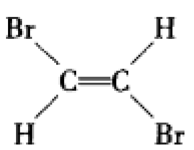
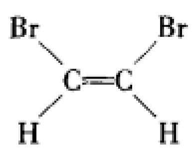
(f) 

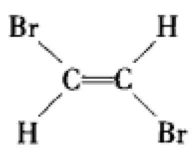
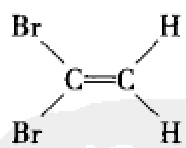
PROBLEM 2-10

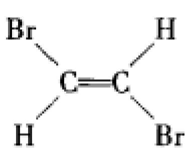
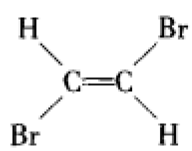
Give the relationship between the following pairs of structures. The possible relationships are

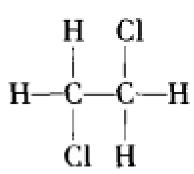
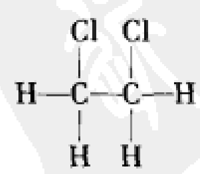
same compound *constitutional isomers (structural isomers)*
cis-trans isomers *not isomers (different molecular formula)*

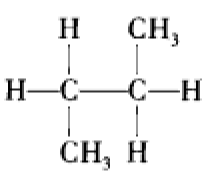
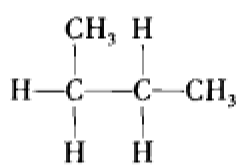
(a) 

(b)  and 

(c)  and 

(d)  and 

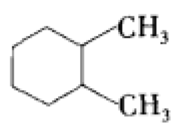
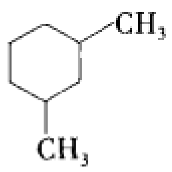
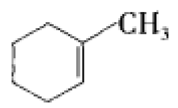
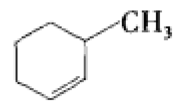
(e)  and 

(f)  and 

(g) $CH_3{-}CH_2{-}CH_2{-}CH_3$ and $CH_3{-}CH{=}CH{-}CH_3$

(h) $CH_2{=}CH{-}CH_2CH_2CH_3$ and $CH_3{-}CH{=}CH{-}CH_2CH_3$

(i) $CH_2{=}CHCH_2CH_2CH_3$ and $CH_3CH_2CH_2CH{=}CH_2$

(j)  and  (k)  and 

2-9 Polarity of Bonds and Molecules

In Section 1-6, we reviewed the concept of polar covalent bonds between atoms with different electronegativities. Now we are ready to combine this concept with molecular geometry to study the polarity of entire molecules.

2-9A Bond Dipole Moments

Bond polarities can range from nonpolar covalent, through polar covalent, to totally ionic. In the following examples, ethane has a nonpolar covalent C—C bond. Methylamine, methanol, and chloromethane have increasingly polar (C—N, C—O, and C—Cl) covalent bonds. Methylammonium chloride ($CH_3NH_3^+Cl^-$) has an ionic bond between the methylammonium ion and the chloride ion.

$H_3C—CH_3$	$H_3C \overset{+\!\longrightarrow}{—} NH_2$	$H_3C \overset{+\!\longrightarrow}{—} OH$	$H_3C \overset{+\!\longrightarrow}{—} Cl$	$H_3\overset{+}{C}NH_3Cl^-$
ethane	methylamine	methanol	chloromethane	methylammonium chloride
(乙烷)	(甲胺)	(甲醇)	(氯甲烷)	(甲基氯化铵)
nonpolar	increasing polarity →			ionic

The polarity of an individual bond is measured as its **bond dipole moment**, μ, defined as

$$\mu = \delta \times d$$

where δ is the amount of charge at either end of the dipole and d is the distance between the charges.

Dipole moments are expressed in units of the **debye** (D) or the coulomb meter (C·m), where 1 debye = 3.34×10^{-30} coulomb meters. If a proton and an electron (charge 1.60×10^{-19} coulomb) were 1 Å apart (distance 10^{-10} meter), the dipole moment would be

$$\mu = (1.60 \times 10^{-19}\ \text{coulomb}) \times (10^{-10}\ \text{meter}) = 1.60 \times 10^{-29}\ \text{coulomb meter}$$

Dipole moments are measured experimentally, and they can be used to calculate other information such as bond lengths and charge separations.

Bond dipole moments in organic compounds range from zero in symmetrical bonds to about 3.6 D for the strongly polar C≡N: triple bond. Table 2-1 shows typical dipole moments for some of the bonds common in organic molecules. Recall that the positive end of the crossed arrow corresponds to the less electronegative (partial positive charge) end of the dipole.

TABLE 2-1 Bond Dipole Moments (Debye) for Some Common Covalent Bonds

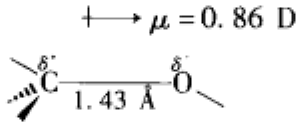
Bond	Dipole Moment, μ	Bond	Dipole Moment, μ
C—N	0.22 D	H—C	0.3 D
C—O	0.86 D	H—N	1.31 D
C—F	1.51 D	H—O	1.53 D
C—Cl	1.56 D	C=O	2.4 D
C—Br	1.48 D	C≡N	3.6 D
C—I	1.29 D		

SOLVED PROBLEM 2-8

Calculate the charge separation for a typical C—O single bond, with a bond length of 1.43 Å and a dipole moment of 0.86 D.

SOLUTION

Using the formula for the dipole moment, we have



$$0.86\ \text{D} = 4.8 \times \delta \times 1.43\ \text{Å}$$
$$\delta = 0.125\ \text{e}$$

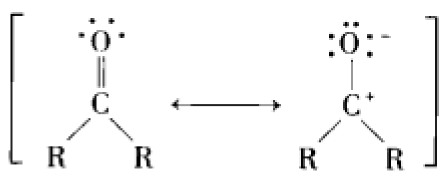
The amount δ of charge separation is about 0.125 electronic charge, so the carbon atom has about an eighth of a positive charge, and the oxygen atom has about an eighth of a negative charge.

PROBLEM 2-11

The C=O double bond has a dipole moment of about 2.4 D and a bond length of about 1.21 Å.

(a) Calculate the amount of charge separation in this bond.

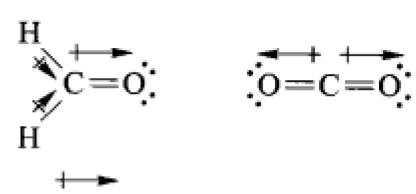
(b) Use this information to evaluate the relative importance of the following two resonance contributors:



2-9B Molecular Dipole Moments

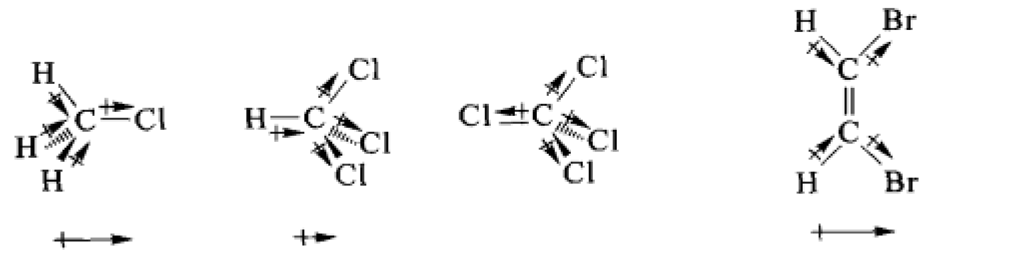
A **molecular dipole moment** is the dipole moment of the molecule taken as a whole. It is a good indicator of a molecule's overall polarity. Molecular dipole moments can be measured directly, in contrast to bond dipole moments, which must be estimated by comparing various compounds. The value of the molecular dipole moment is equal to the *vector* sum of the individual bond dipole moments. This vector sum reflects both the magnitude and the direction of each individual bond dipole moment.

For example, formaldehyde has one strongly polar C=O bond, and carbon dioxide has two. We might expect CO_2 to have the larger dipole moment, but its dipole moment is actually zero. The symmetry of the carbon dioxide molecule explains this surprising result. The structures of formaldehyde and carbon dioxide are shown here. In carbon dioxide, the bond dipole moments are oriented in opposite directions, and they cancel each other.



$\mu = 2.3$ D — formaldehyde $\mu = 0$ — carbon dioxide

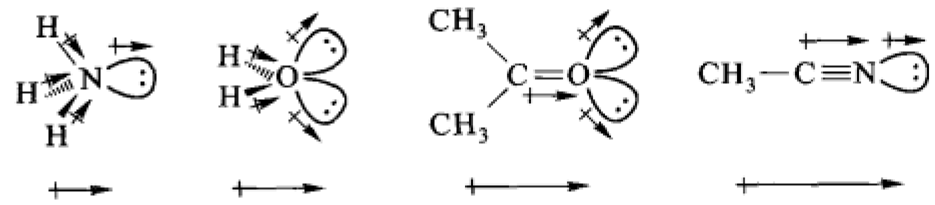
Figure 2-21 shows some examples of molecular dipole moments. Notice that the dipole moment of C—H bonds is small, so we often treat C—H bonds as nearly nonpolar. Also note that the tetrahedral symmetry of CCl_4 positions the four C—Cl dipole moments in directions so that they cancel. A partial canceling of the bond dipole moments explains why $CHCl_3$, with three C—Cl bonds, has a smaller molecular dipole moment than CH_3Cl, with only one.



$\mu = 1.9$ D chloromethane (氯甲烷) | $\mu = 1.0$ D chloroform (氯仿) | $\mu = 0$ carbon tetrachloride (四氯化碳) | $\mu = 1.9$ D *cis*-1,2-dibromoethene (顺-1,2-二溴乙烯)

Figure 2-21 Molecular dipole moments. A molecular dipole moment is the vector sum of the individual bond dipole moments.

Lone pairs of electrons contribute to the dipole moments of bonds and molecules. Each lone pair corresponds to a charge separation, with the nucleus having a partial positive charge balanced by the negative charge of the lone pair. Figure 2-22 shows four molecules with lone pairs and large dipole moments. Notice how the lone pairs contribute to the large dipole moments, especially in the C=O and C≡N bonds.



$\mu = 1.5$ D ammonia (氨) | $\mu = 1.9$ D water | $\mu = 2.9$ D acetone (丙酮) | $\mu = 3.9$ D acetonitrile (乙腈)

Figure 2-22 Effects of lone pairs. Lone pairs may have large effects on molecular dipole moments.

PROBLEM 2-12

The N—F bond is more polar than the N—H bond, but NF_3 has a *smaller* dipole moment than NH_3. Explain this curious result.

$$\begin{array}{cc} NH_3 & NF_3 \\ \mu = 1.5\ D & \mu = 0.2\ D \end{array}$$

PROBLEM 2-13

For each of the following compounds

1. Draw the structure.
2. Show how the bond dipole moments (and those of any nonbonding pairs of electrons) contribute to the molecular dipole moment.
3. Predict whether the compound has a large (> 1 D), small, or zero dipole moment.

(a) CH_2Cl_2 **(b)** CH_3F **(c)** CF_4 **(d)** CH_3OH
(e) O_3 **(f)** HCN **(g)** CH_3CHO **(h)** $H_2C{=}NH$
(i) $(CH_3)_3N$ **(j)** $CH_2{=}CHCl$ **(k)** BF_3 **(l)** $BeCl_2$
(m) NH_4^+

PROBLEM 2-14

Two isomers of 1,2-dichloroethene are known. One has a dipole moment of 2.4 D; the other has zero dipole moment. Draw the two isomers and explain why one has zero dipole moment.

CHCl=CHCl
1,2-dichloroethene (1,2-二氯乙烯)

2–10 Intermolecular Forces

When two molecules approach, they attract or repel each other. This interaction can be described fairly simply in the case of atoms (like the noble gases) or simple molecules such as H_2 or Cl_2. In general, the forces are attractive until the molecules come so close that they infringe on each other's atomic radius. When this happens, the small attractive force quickly becomes a large repulsive force, and the molecules "bounce" off each other. With complicated organic molecules, these attractive and repulsive forces are more difficult to predict. We can still describe the nature of the forces, however, and we can show how they affect the physical properties of organic compounds.

Attractions between molecules are particularly important in solids and liquids. In these "condensed" phases, the molecules are continuously in contact with each other. The melting points, boiling points, and solubilities of organic compounds show the effects of these forces. Three major kinds of attractive forces cause molecules to associate into solids and liquids: the dipole-dipole forces of polar molecules, the London forces that affect all molecules, and the "hydrogen bonds" that link molecules having —OH or —NH groups.

2–10A Dipole-Dipole Forces

Most molecules have permanent dipole moments as a result of their polar bonds. Each molecular dipole moment has a positive end and a negative end. The most stable arrangement has the positive end of one dipole close to the negative end of another. When two negative ends or two positive ends approach each other, they repel, but they may turn and orient themselves in the more stable positive-to-negative arrangement. **Dipole-dipole forces**, therefore, are generally attractive intermolecular forces resulting from the attraction of the positive and negative ends of the dipole moments of polar molecules. Figure 2–23 shows the attractive and repulsive orientations of polar molecules, using chloromethane as the example.

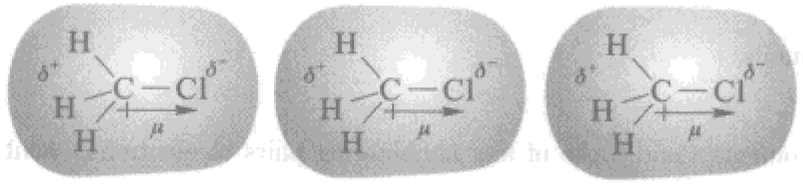
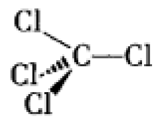


Figure 2–23 Dipole-dipole interactions. Dipole-dipole interactions result from the approach of two polar molecules. In a liquid or a solid, the molecules are mostly oriented with the positive and negative ends together, and the net force is attractive.

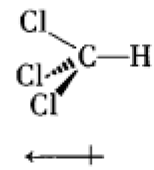
Polar molecules are mostly oriented in the lower-energy positive-to-negative arrangement, and the net force is attractive. This attraction must be overcome when the liquid vaporizes, resulting in larger heats of vaporization and higher boiling points for strongly polar compounds.

2–10B The London Dispersion Force

Carbon tetrachloride (CCl_4) has zero dipole moment, yet its boiling point is higher than that of chloroform (μ = 1.0 D). Clearly, there must be some kind of force other than dipole-dipole forces holding the molecules of carbon tetrachloride together.



$\mu = 0$
carbon tetrachloride, bp = 77 ℃



$\mu = 1.0$ D
chloroform, bp = 62 ℃

In nonpolar molecules such as carbon tetrachloride, the principal attractive force is the **London dispersion force**, one of the **van der Waals forces** (Figure 2–24). The London force arises from temporary dipole moments that are induced in a molecule by other nearby molecules. Even though carbon tetrachloride has no permanent dipole moment, the electrons are not always evenly distributed. A small temporary dipole moment is induced when one molecule approaches another molecule in which the electrons are slightly displaced from a symmetrical arrangement. The electrons in the approaching molecule are displaced slightly so that an attractive dipole-dipole interaction results.

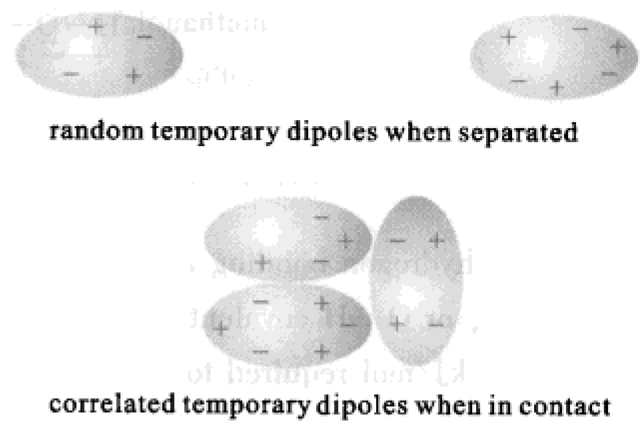
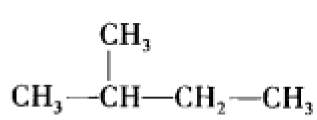


Figure 2–24 London dispersion forces. London dispersion forces result from the attraction of correlated temporary dipoles.

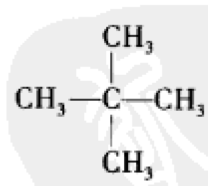
These temporary dipoles last only a fraction of a second, and they change continuously; yet they are correlated so their net force is attractive. This attractive force depends on close surface contact of two molecules, so it is roughly proportional to the molecular surface area. Carbon tetrachloride has a larger surface area than chloroform (a chlorine atom is much larger than a hydrogen atom), so the intermolecular van der Waals attractions between carbon tetrachloride molecules are stronger than they are between chloroform molecules.

We can see the effects of London forces in the boiling points of simple hydrocarbons. If we compare the boiling points of several different isomers, the isomers with larger surface areas (and greater potential for London force attraction) have higher boiling points. The boiling points of three isomers of molecular formula C_5H_{12} are given here. The long-chain isomer (n-pentane) has the greatest surface area and the highest boiling point. As the amount of chain branching increases, the molecule becomes more spherical and its surface area decreases. The most highly branched isomer (neopentane) has the smallest surface area and the lowest boiling point.

n-pentane, bp = 36 ℃
(正戊烷)



isopentane, bp = 28 ℃
(异戊烷)



neopentane, bp = 10 ℃
(新戊烷)

2–10C Hydrogen Bonding

A **hydrogen bond** is not a true bond but a particularly strong dipole-dipole attraction. A hydrogen atom can participate in hydrogen bonding if it is bonded to oxygen, nitrogen, or fluorine. Organic compounds do not contain H—F bonds, so we consider only N—H and O—H hydrogens to be hydrogen bonded (Figure 2–25).

The O—H and N—H bonds are strongly polarized, leaving the hydrogen atom with a partial positive charge. This electrophilic hydrogen has a strong affinity for nonbonding electrons, and it forms intermolecular attachments with the nonbonding electrons on oxygen or nitrogen atoms.

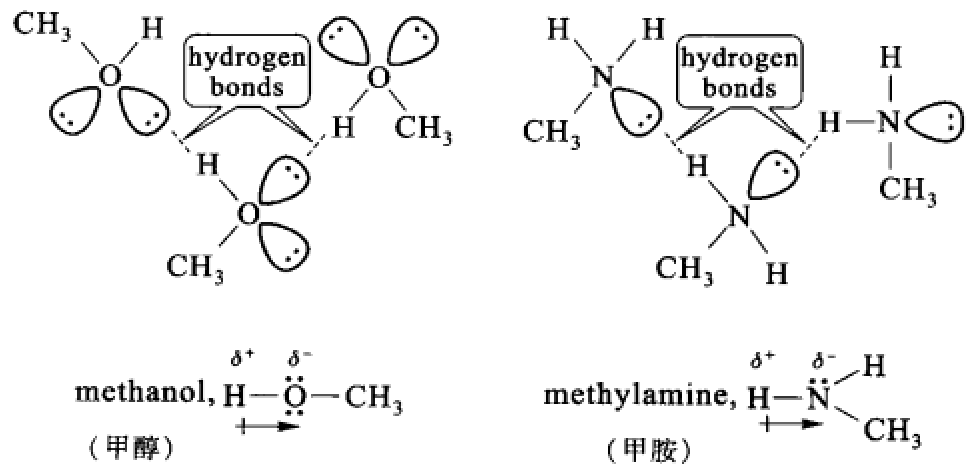


Figure 2−25 Hydrogen bonding. Hydrogen bonding is a strong intermolecular attraction between an electrophilic O—H or N—H hydrogen atom and a pair of nonbonding electrons.

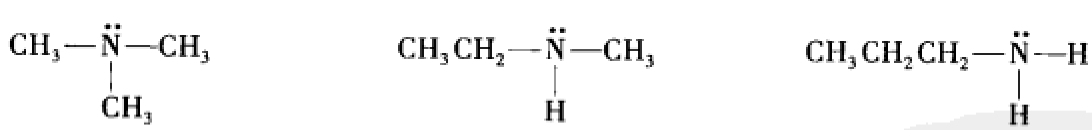
Although hydrogen bonding is a strong form of intermolecular attraction, it is much weaker than a normal C—H, N—H, or O—H covalent bond. Breaking a hydrogen bond requires about 5 20 kJ/mol, compared with about 100 400 kJ/mol required to break a C—H, N—H, or O—H bond.

Hydrogen bonding has a large effect on the physical properties of organic compounds, as shown by the boiling points of ethanol (ethyl alcohol) and dimethyl ether, two isomers of molecular formula C_2H_6O:

$CH_3—CH_2—OH$	$CH_3—O—CH_3$
ethanol, bp 78 ℃	dimethyl ether, bp −25 ℃
(乙醇)	(甲醚)

These two isomers have the same size and the same molecular weight. Alcohols like ethanol have O—H hydrogens, however, so they are extensively hydrogen bonded. Dimethyl ether has no O—H hydrogen, so it cannot form hydrogen bonds. As a result of its hydrogen bonding, ethanol has a boiling point more than 100 ℃ higher than that of dimethyl ether.

The effect of N—H hydrogen bonding on boiling points can be seen in the isomers of formula C_3H_9N shown below. Trimethylamine has no N—H hydrogens, so it is not hydrogen bonded. Ethylmethylamine has one N—H hydrogen atom, and the resulting hydrogen bonding raises its boiling point about 34 ℃ above that of trimethylamine. Propylamine, with two N—H hydrogens, is more extensively hydrogen bonded and has the highest boiling point of these three isomers.



trimethylamine, bp 3.5 ℃	ethylmethylamine, bp 37 ℃	propylamine, bp 49 ℃
(三甲胺)	(甲基乙基胺)	(丙胺)

Alcohols form stronger hydrogen bonds than amines, probably because oxygen is more electronegative than nitrogen. Thus, the O—H bond is more strongly polarized than the N—H bond. This effect is seen in the boiling points of the preceding isomers, with more than 100° difference in the boiling points of ethanol and dimethyl ether, compared with a 34° difference for ethylmethylamine and trimethylamine.

PROBLEM 2−15

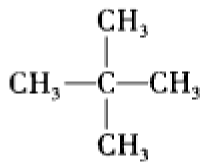
Draw the hydrogen bonding that takes place between

(a) two molecules of ethanol.

(b) two molecules of propylamine.

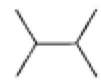
SOLVED PROBLEM 2-9

Rank the following compounds in order of increasing boiling points. Explain the reasons for your chosen order.



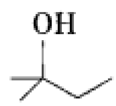
neopentane
（新戊烷）

n-hexane
（正己烷）



2,3-dimethylbutane
（2,3-二甲基丁烷）

pentan-1-ol
（1-戊醇）



2-methylbutan-2-ol
（2-甲基-2-丁醇）

SOLUTION

To predict relative boiling points, we should look for differences in (1) hydrogen bonding, (2) molecular weight and surface area, and (3) dipole moments. Except for neopentane, these compounds have similar molecular weights. Neopentane is the lightest, and it is a compact spherical structure that minimizes van der Waals attractions. Neopentane is the lowest-boiling compound.

Neither *n*-hexane nor 2,3-dimethylbutane is hydrogen bonded, so they will be next higher in boiling points. Because 2,3-dimethylbutane is more highly branched (and has a smaller surface area) than *n*-hexane, 2,3-dimethylbutane will have a lower boiling point than *n*-hexane. So far, we have

neopentane < 2,3-dimethylbutane < *n*-hexane < the others

The two remaining compounds are both hydrogen-bonded, and pentan-1-ol has more area for van der Waals forces. Therefore, pentan-1-ol should be the highest-boiling compound. We predict the following order:

neopentane	<	2,3-dimethylbutane	<	*n*-hexane	<	2-methylbutan-2-ol	<	pentan-1-ol
10 ℃		58 ℃		69 ℃		102 ℃		138 ℃

The actual boiling points are given here to show that our prediction is correct.

PROBLEM 2-16

For each pair of compounds, circle the compound you expect to have the higher boiling point. Explain your reasoning.

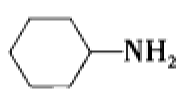
(a) $(CH_3)_3C—C(CH_3)_3$ and $(CH_3)_2CH—CH_2CH_2—CH(CH_3)_2$

(b) $CH_3(CH_2)_6CH_3$ and $CH_3(CH_2)_5CH_2OH$

(c) $HOCH_2—(CH_2)_4—CH_2OH$ and $(CH_3)_3CCH(OH)CH_3$

(d) $(CH_3CH_2CH_2)_2NH$ and $(CH_3CH_2)_3N$

(e)

and 

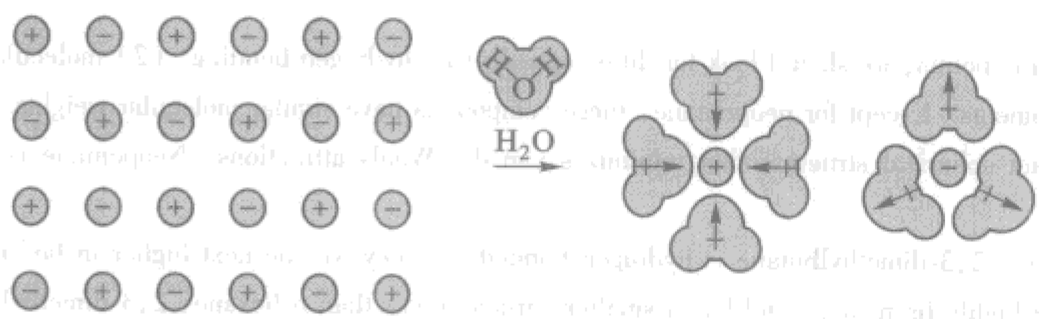
2-11 Polarity Effects on Solubilities

In addition to affecting boiling points and melting points, intermolecular forces determine the solubility properties of organic compounds. The general rule is that "*like dissolves like.*" Polar substances dissolve in polar solvents, and nonpolar substances dissolve in nonpolar solvents. We discuss the reasons for this rule now, then apply the

rule in later chapters as we discuss the solubility properties of organic compounds.

We should consider four different cases: (1) a polar solute with a polar solvent, (2) a polar solute with a nonpolar solvent, (3) a nonpolar solute with a nonpolar solvent, and (4) a nonpolar solute with a polar solvent. We will use sodium chloride and water as examples of polar solutes and solvents, and paraffin "wax" and gasoline as examples of nonpolar solutes and solvents.

Polar Solute in a Polar Solvent (Dissolves) When you think about sodium chloride dissolving in water, it seems remarkable that the oppositely charged ions can be separated from each other. A great deal of energy is required to separate these ions. A polar solvent (such as water) can separate the ions because it *solvates* them (Figure 2−26). If water is the solvent, the solvation process is called *hydration*. As the salt dissolves, water molecules surround each ion, with the appropriate end of the water dipole moment next to the ion. In the case of the positive (sodium) ion, the oxygen atom of the water molecule approaches. The negative ions (chloride) are approached by the hydrogen atoms of the water molecules.



ionic crystal lattice (离子晶格) hydrated ions (dissolves) (水合离子)

Figure 2−26 Polar solute in water (a polar solvent). The hydration of sodium and chloride ions by water molecules overcomes the lattice energy of sodium chloride. The salt dissolves.

Because water molecules are strongly polar, a large amount of energy is released when the sodium and chloride ions are hydrated. This energy is nearly sufficient to overcome the lattice energy of the crystal. The salt dissolves, partly because of strong solvation by water molecules and partly because of the increase in entropy (randomness or freedom of movement) when it dissolves.

Polar Solute in a Nonpolar Solvent (Does Not Dissolve) If you stir sodium chloride with a nonpolar solvent such as turpentine or gasoline, you will find that the salt does not dissolve. The nonpolar molecules of these solvents do not solvate ions very strongly, and they cannot overcome the large lattice energy of the salt crystal. This is a case where the attractions of the ions in the solid for each other are much greater than their attractions for the solvent.

Nonpolar Solute in a Nonpolar Solvent (Dissolves) Paraffin "wax" dissolves in gasoline. Both paraffin and gasoline are mixtures of nonpolar hydrocarbons. The molecules of a nonpolar substance (paraffin) are weakly attracted to each other, and these van der Waals attractions are easily overcome by van der Waals attractions with the solvent. Although there is little change in energy when the nonpolar substance dissolves in a nonpolar solvent, there is a large increase in entropy.

Nonpolar Solute in a Polar Solvent (Does Not Dissolve) Anyone who does home canning knows that a nonpolar solid such as paraffin does not dissolve in a polar solvent such as water. Why not? The nonpolar molecules are only weakly attracted to each other, and little energy is required to separate them. The problem is that the water molecules are strongly attracted to each other by their hydrogen bonding. If a nonpolar paraffin molecule were to dissolve, the water molecules around it would have to form a cavity. Water molecules at the edge of the

cavity have fewer available neighbors for hydrogen bonding, resulting in a tighter, more rigid, ice-like structure around the cavity. This tighter structure results in an unfavorable decrease in the entropy of the system: $\Delta G = \Delta H - T\Delta S$, and ΔH is small in most cases. Therefore, the negative value of ΔS makes ΔG positive (unfavorable), and the nonpolar substance does not dissolve.

This general rule "like dissolves like" also applies to the mixing of liquids. Everyone knows that water and gasoline (or oil) do not mix. Gasoline and oil are both nonpolar hydrocarbons, however, and they mix freely with each other. They do not dissolve in water because they would have to break up the hydrogen bonds of the water molecules.

Ethanol is a polar molecule, and it is miscible with water, that is, it mixes freely with water in all proportions. Ethanol has an O—H group that forms hydrogen bonds with water molecules. When ethanol dissolves in water, it forms new ethanol-water hydrogen bonds to replace the water-water and ethanol-ethanol hydrogen bonds that are broken.

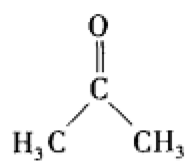
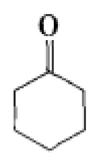
PROBLEM 2-17

Circle the member of each pair that is more soluble in water.

(a) $CH_3CH_2OCH_2CH_3$ or $CH_3CH_2CH_2CH_2CH_3$

(b) $CH_3CH_2NHCH_3$ or $CH_3CH_2CH_2CH_3$

(c) CH_3CH_2OH or $CH_3CH_2CH_2CH_2OH$

(d)  or 

Summary in Chinese

本 章 概 要

一、分子轨道理论(molecular orbital theory)

1. 基本概念：量子化学用波函数表示原子轨道(ϕ)和分子轨道(ψ)，波函数的平方代表原子或分子轨道中电子出现的概率。两个原子轨道线性组合得到两个分子轨道(linear combination of atomic orbitals)。其中一个分子轨道是由两个原子轨道的波函数相加组成，称为成键分子轨道(bonding molecular orbital)，能量低于线性组合前的原子轨道，而另一个分子轨道是由两个原子轨道的波函数相减组成，称为反键分子轨道(antibonding molecular orbital)，能量高于线性组合前的原子轨道。在基态分子中，反键分子轨道中通常未填充电子。分子轨道中的电子排布原则与原子轨道相同。分子轨道理论常用来解释共轭不饱和有机化合物的性质，如稳定性和反应活性。

2. σ 键与 π 键：两原子的 s 与 s 轨道重叠、s 与 p 轨道重叠，两个 p 轨道"头对头"重叠形成 σ 键，有机化合物中所有单键都是 σ 键；两原子的 p 轨道"肩并肩"相互重叠则形成 π 键。双键和三键中除有一个 σ 键之外，双键中有一个 π 键，而三键中有两个相互垂直的 π 键。单键可绕键轴旋转，而双键是刚性的，不能绕 σ 键轴旋转，如强行旋转，π 键将断裂。由此导致烯烃的顺-反异构现象。

二、价键理论(valence bond theory)

1. 价壳层电子对排斥理论(valence-shell electron-pair repulsion theory)：由于电子对相互排斥，在中心原子周围的键与键、键与孤对电子之间总是彼此保持空间上可能的最大平均角度，达到最大分开距离，最

小排斥作用。

2. 杂化原子轨道(hybrid atomic orbital):在形成分子轨道之前,一个原子中能量相近的原子轨道可进行杂化,形成能量相等的杂化轨道,其数目与参与杂化的原子轨道数目相等。杂化碳原子轨道分为三种:sp^3 杂化给出四个杂化轨道,形成四面体结构,四个杂化轨道相互间夹角约 109.5°;sp^2 杂化给出三个杂化轨道,形成平面三角形结构,三个杂化轨道相互间夹角为 120°,未参与杂化的 p_z 轨道与三个 sp^2杂化轨道所在平面垂直;sp 杂化给出两个杂化轨道,形成直线形结构,两个杂化轨道间夹角为 180°,两个 sp 杂化轨道都垂直于未参与杂化的 p_y 和 p_z 轨道所在的平面。所有带未成对电子的杂化轨道均能与其他原子形成 σ 键,而带未成对电子的未参与杂化的 p 轨道则能与相邻的其他原子中与其平行的 p 轨道形成 π 键。

3. 三维结构式(three-dimensional formula):价键理论可用来直观地解释有机分子的构型。一般用三维结构式表示有机分子的立体结构。

三、同分异构(isomerism)

1. 同分异构体(isomer):具有相同分子式,但结构和性质不同的化合物。这些化合物互为同分异构体,简称异构体。同分异构体可分为两大类:构造异构体和立体异构体。

2. 构造异构体(constitutional isomer or structural isomer):分子式相同的化合物,由于分子中原子成键顺序不同所产生的异构体称为构造异构体。构造异构体可分为 5 种类型:碳骨架异构,双键或三键位置异构,取代基或官能团位置异构,官能团异构,互变异构。

3. 立体异构体(stereoisomer):分子式相同且分子中原子成键顺序也相同的化合物,由于分子中原子或基团的空间排列方式不同所产生的异构体称为立体异构体。立体异构体可分为两大类:对映异构体和非对映异构体。烯烃和环状化合物的顺-反异构体(cis-trans isomer),亦称为几何异构体(geometric isomer),属于立体异构中的非对映异构体。

四、键和分子的极性 (polarity of bonds and molecules)

1. 极性共价键(polar covalent bond):在极性共价键中,成键电子云非对称地分布在两原子核周围,电负性较大的原子一端带部分负电荷(δ^-),而电负性较小的原子一端带部分正电荷(δ^+)。键的极性强弱可由键偶极矩来衡量。共价键的极性直接影响有机化合物的物理性质和化学反应活性。

2. 键偶极矩(bond dipole moment):极性键正电中心或负电中心上的电荷值(q,单位: C)与两个电荷中心之间的距离(d,单位: m)的乘积称为键偶极矩(μ,单位: C·m),在本书中也用 Debye(D)表示,用来度量键的极性强弱。键偶极矩为矢量,用" +→ 表示,箭头指向键的负电荷一端。

3. 分子偶极矩(molecular dipole moment):分子的极性强弱由分子偶极矩来衡量。分子偶极矩为构成分子的化学键的键偶极矩的矢量之和。分子中原子上的孤对电子可使分子偶极矩增强。

五、分子间作用力对化合物物理性质的影响 (influences of intermolecular forces on the physical property of compounds)

1. 分子间作用力:

● 偶极-偶极作用(dipole-dipole force):极性分子偶极矩间的相互作用,大小取决于分子的极性。

● 伦敦色散力(the London dispersion force):分子中由于电子运动产生的瞬时偶极矩间的相互作用,大小取决于分子的极化率和分子的表面积。色散力和偶极-偶极作用力统称为范德华力(van der Waals force)。

● 氢键(hydrogen bond):与 F、O、N 等电负性强且原子半径小的原子成键的氢具有一定的电正性,能与带部分负电荷的 F、O、N 等原子形成氢键。氢键为强的分子间力,但比正常的键弱得多。

2. 影响有机化合物沸点的主要因素:

● 相对分子质量大小:极性相似的化合物,沸点随相对分子质量增大而升高。

● 分子极性强弱:相对分子质量相似的化合物,沸点随分子极性增强而升高。

● 分子表面积:相对分子质量和极性都相似的化合物,沸点随分子表面积增大而升高。

● 能否形成氢键:相对分子质量相似的化合物,能形成分子间氢键的化合物沸点明显升高,分子间氢键越多,沸点越高。

3. 分子极性对有机化合物溶解度的影响:化合物在不同溶剂中的溶解性可概括为“相似相溶”,即极性化合物可溶于极性溶剂,非极性化合物可溶于非极性溶剂,而极性化合物难溶于非极性溶剂,反之亦然。从实质上说,如果有机化合物分子与溶剂分子之间的作用力相似于化合物分子之间和溶剂分子之间的作用力时,则化合物能溶于此种溶剂,否则就难以溶解。

Essential Problem-Solving Skills in Chapter 2

1. Draw the structure of a single bond, a double bond, and a triple bond.
2. Predict the hybridization and geometry of the atoms in a molecule.
3. Draw a three-dimensional representation of a given molecule.
4. Identify constitutional isomers and stereoisomers.
5. Identify polar and nonpolar molecules, and predict which ones can engage in hydrogen bonding.
6. Predict general trends in the boiling points and solubilities of compounds, based on their size, polarity, and hydrogen-bonding ability.

Study Problems

2-18 Define and give examples of the following terms:

(a) bonding MO (成键分子轨道)
(b) antibonding MO (反键分子轨道)
(c) hybrid atomic orbital (杂化原子轨道)
(d) sigma bond
(e) pi bond
(f) double bond
(g) triple bond
(h) constitutional isomers (构造异构)
(i) cis-trans isomers (顺-反异构)
(j) stereoisomers (立体异构)
(k) bond dipole moment (键偶极矩)
(l) molecular dipole moment (分子偶极矩)
(m) dipole-dipole forces (偶极-偶极间力)
(n) the London dispersion forces
(o) hydrogen bonding (氢键)
(p) miscible liquids (互溶液体)

2-19 If the carbon atom in CH_2Cl_2 were flat, there would be two stereoisomers. The carbon atom in CH_2Cl_2 is actually tetrahedral. Draw a three-dimensional structure, and determine whether there are any stereoisomers of CH_2Cl_2.

2-20 Cyclopropane (C_3H_6, a three-membered ring) is more reactive than most other cycloalkanes.

(a) Draw a Lewis structure for cyclopropane.
(b) Compare the bond angles of the carbon atoms in cyclopropane with those in an acyclic (noncyclic) alkane.
(c) Suggest why cyclopropane is so reactive.

2-21 For each of the following compounds,

1. Give the hybridization and approximate bond angles around each atom except hydrogen.
2. Draw a three-dimensional diagram, including any lone pairs of electrons.

(a) H_3O^+
(b) ^-OH
(c) NH_2NH_2
(d) $(CH_3)_3N$
(e) $(CH_3)_4N^+$
(f) CH_3COOH
(g) $CH_3CH{=}NH$
(h) CH_3OH
(i) CH_2O

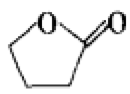
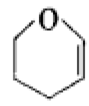
2-22 For each of the following compounds,

1. Draw a Lewis structure.
2. Show the kinds of orbitals that overlap to form each bond.

3. Give approximate bond angles around each atom except hydrogen.

(**a**) $(CH_3)_2NH$ (**b**) CH_3CH_2OH (**c**) $CH_3—CH═N—CH_3$

(**d**) $CH_3—CH═C(CH_3)_2$ (**e**) $CH_3—C≡C—CHO$ (**f**) $H_2N—CH_2—CN$

(**g**) $CH_3—\overset{\overset{O}{\|}}{C}—CH_3$ (**h**)  (**i**) 

2-23 In most amines, the nitrogen atom is sp^3 hybridized, with a pyramidal structure and bond angles close to 109°. In formamide, the nitrogen atom is found to be planar, with bond angles close to 120°. Explain this surprising finding. (*Hint*: Consider resonance forms and the overlap needed in them.)

$$H—\overset{\overset{O}{\|}}{C}—\ddot{N}H_2$$

formamide（甲酰胺）

2-24 Predict the hybridization and geometry of the carbon and nitrogen atoms in the following ions. (*Hint*: Resonance.)

(**a**) $CH_3—\overset{\overset{O}{\|}}{C}—\overset{-}{\ddot{C}}H_2$ (**b**) $H_2N—CH═CH—\overset{+}{C}H_2$

2-25 Draw orbital pictures of the pi bonding in the following compounds:

(**a**) CH_3COCH_3 (**b**) HCN (**c**) $CH_2═CH—CH═CH—CN$

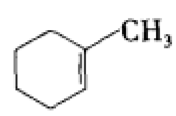
(**d**) $CH_3—C≡C—CHO$

2-26 (**a**) Draw the structure of *cis*-$CH_3—CH═CH—CH_2CH_3$ showing the pi bond with its proper geometry.

(**b**) Circle the six coplanar atoms in this compound.

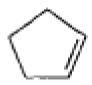
(**c**) Draw the trans isomer, and circle the coplanar atoms. Are there still six?

(**d**) Circle the coplanar atoms in the following structure.



2-27 Which of the following compounds show cis-trans isomerism? Draw the cis and trans isomers of the ones that do.

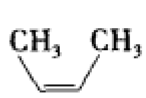
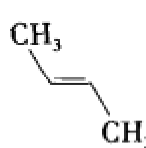
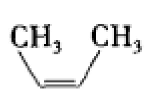
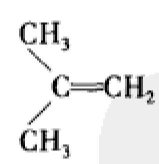
(**a**) $CH_3CH═CHCH_3$ (**b**) $CH_3—C≡C—CH_3$ (**c**) $CH_2═C(CH_3)_2$

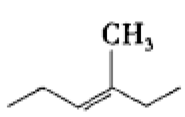
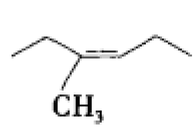
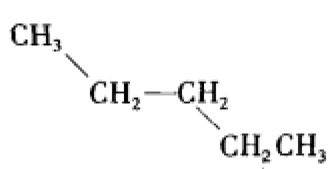
(**d**) cyclopentene,  (环戊烯)

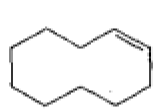
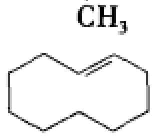
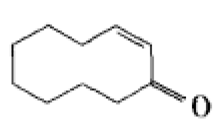
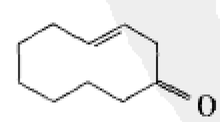
(**e**) $CH_3—CH═\underset{\underset{CH_2CH_2CH_3}{|}}{C}—CH_2—CH_3$

2-28 Give the relationships between the following pairs of structures. The possible relationships are: same compound, cis-trans isomers, constitutional (structural) isomers, not isomers (different molecular formula).

(**a**) $CH_3CH_2CH_2CH_3$ and $(CH_3)_3CH$ (**b**) $CH_2═CH—CH_2Cl$ and $CHCl═CH—CH_3$

(**c**)  and  (**d**)  and 

(**e**)  and  (**f**)  and

(**g**)  and  (**h**)  and 

2-29 Sulfur dioxide has a dipole moment of 1.60 D. Carbon dioxide has a dipole moment of zero, even though C—O bonds are more polar than S—O bonds. Explain this apparent contradiction.

2-30 For each of the following compounds,

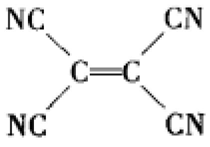
1. Draw the Lewis structure.

2. Show how the bond dipole moments (and those of any nonbonding pairs of electrons) contribute to the molecular dipole

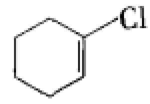
moment.

3. Predict whether the compound will have a large (>1 D), small, or zero dipole moment.

(a) $CH_3—CH{=}N—CH_3$ (b) $CH_3—CN$ (c) CBr_4 (d) $CH_3—C(=O)—CH_3$

(e) 

(f)

(g) 

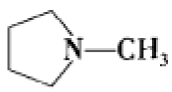
2-31 Diethyl ether and 1-butanol are isomers, and they have similar solubilities in water. Their boiling points are very different, however. Explain why these two compounds have similar solubility properties but dramatically different boiling points.

$CH_3CH_2—O—CH_2CH_3$	$CH_3CH_2CH_2CH_2—OH$
diethyl ether, bp 35 ℃	1-butanol, bp 118 ℃
8.4 mL dissolves in 100 mL H_2O	9.1 mL dissolves in 100 mL H_2O

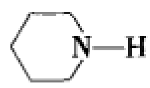
2-32 *N*-methylpyrrolidine has a boiling point of 81 ℃, and piperidine has a boiling point of 106 ℃.

(a) Explain this large difference (25 ℃) in boiling point for these two isomers.

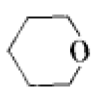
(b) Tetrahydropyran has a boiling point of 88 ℃, and cyclopentanol has a boiling point of 141 ℃. These two isomers have a boiling point difference of 53 ℃. Explain why the two oxygen-containing isomers have a much larger boiling point difference than the two amine isomers.



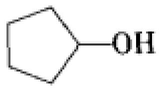
N-methylpyrrolidine, bp 81 ℃
(*N*-甲基吡咯烷)



piperidine, bp 106 ℃
(哌啶)



tetrahydropyran, bp 88 ℃
(四氢吡喃)



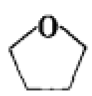
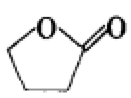
cyclopentanol, bp 141 ℃
(环戊醇)

2-33 Which of the following pure compounds can form hydrogen bonds? Which can form hydrogen bonds with water?

(a) $(CH_3CH_2)_2NH$ (b) $(CH_3CH_2)_3N$ (c) $CH_3CH_2CH_2OH$

(d) $(CH_3CH_2CH_2)_2O$ (e) $CH_3(CH_2)_3CH_3$ (f) $CH_2{=}CH—CH_2CH_3$

(g) CH_3COCH_3 (h) CH_3CH_2COOH (i) CH_3CH_2CHO

(j)  (k)  (l) $CH_3—C(=O)—NH_2$

2-34 Predict which compound in each pair has the higher boiling point. Explain your prediction.

(a) $CH_3CH_2OCH_3$ or $CH_3CH(OH)CH_3$ (b) $CH_3CH_2CH_2CH_3$ or $CH_3CH_2CH_2CH_2CH_3$

(c) $CH_3CH_2CH_2CH_2CH_3$ or $(CH_3)_2CHCH_2CH_3$ (d) $CH_3CH_2CH_2CH_2CH_3$ or $CH_3CH_2CH_2CH_2CH_2Cl$

2-35 Dimethyl sulfoxide (DMSO) has been used as an anti-inflammatory rub for racehorses. DMSO and acetone seem to have similar structures, but the C=O carbon atom in acetone is planar, while the S=O sulfur atom in DMSO is pyramidal. Draw correct Lewis structures for DMSO and acetone, predict the hybridizations, and explain these observations.

$CH_3—S(=O)—CH_3$	$CH_3—C(=O)—CH_3$
DMSO (二甲基亚砜)	acetone (丙酮)

Chapter 3

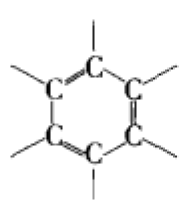
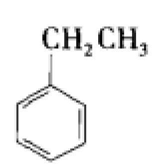
Brief Introduction and Nomenclature of Organic Compounds

The number of organic compounds is virtually limitless. This vast number of compounds is normally classified by their functional groups because chemical reactions occur at the functional group and compounds with the same functional group have similar reactivity. In this chapter, we will have a brief look of organic compounds and learn how to name compounds by a systematic method, so that you can recognize the functional groups and know the names of the compounds as you encounter them in the future chapters. For the purpose of this brief survey, we divide organic compounds into three classes: (1) hydrocarbons, (2) compounds containing oxygen, and (3) compounds containing nitrogen.

3-1 Hydrocarbons

The **hydrocarbons** are compounds composed entirely of carbon and hydrogen. We classify hydrocarbons according to their bonding as shown in Table 3-1. Alkanes have only single bonds. A hydrocarbon with a carbon-carbon double bond (such as ethylene) is an *alkene*. If a hydrocarbon has a carbon-carbon triple bond (like acetylene), it is an *alkyne*. Hydrocarbons with aromatic rings (resembling benzene) are called *aromatic hydrocarbons*.

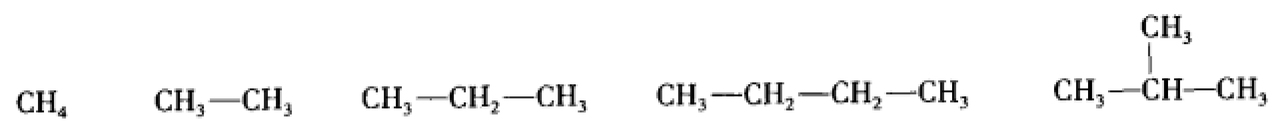
TABLE 3-1 Summary of Hydrocarbon Classification

Compound Type	Functional Group	Example
alkanes (烷烃)	none (no double or triple bonds)	$CH_3—CH_2—CH_3$, propane (丙烷)
alkenes (烯烃)	$>C=C<$ double bond	$CH_2=CH—CH_3$, propene (丙烯)
alkynes (炔烃)	$—C\equiv C—$ triple bond	$H—C\equiv C—CH_3$, propyne (丙炔)
aromatics (芳烃)	benzene ring 	 , ethylbenzene (乙基苯)

A hydrocarbon with no double or triple bonds is said to be **saturated** because it has the maximum number of bonded hydrogens. Another way to describe *alkanes*, then, is as the class of **saturated hydrocarbons**. Hydrocarbons with double and/or triple bonds are called unsaturated compounds.

3-1A Alkanes

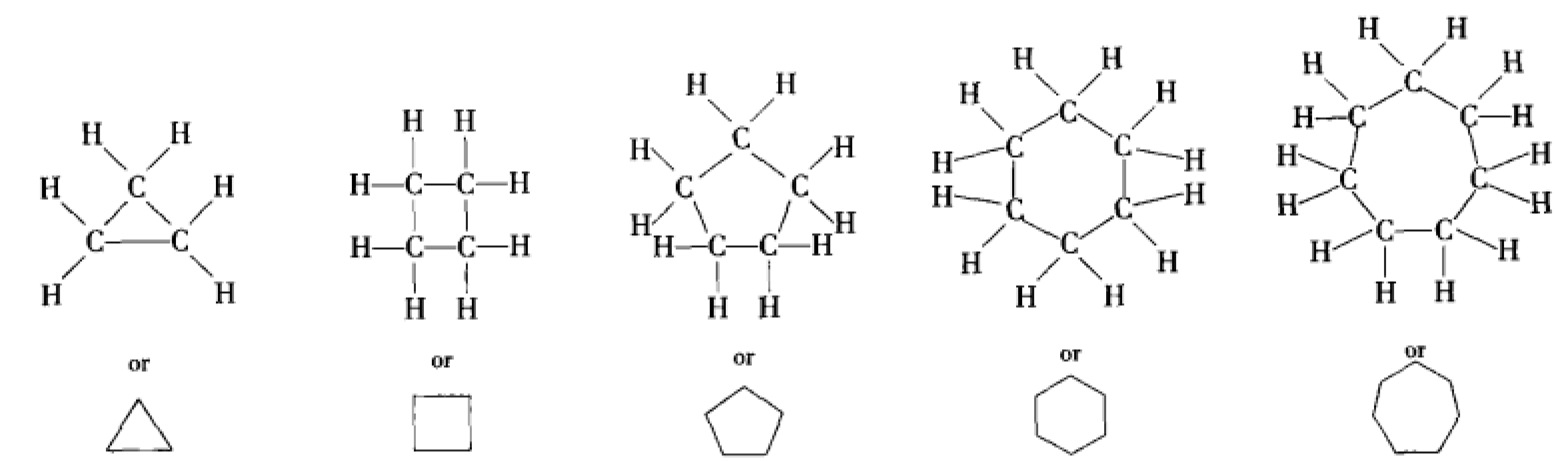
Alkanes are hydrocarbons that contain only single bonds. Alkane names generally have the *-ane* suffix, and the first part of the name gives the number of carbon atoms.



methane (甲烷)　ethane (乙烷)　propane (丙烷)　butane (丁烷)　isobutane (异丁烷)

Alkanes are the major components of heating gases (natural gas and liquefied petroleum gas), gasoline, motor oil, fuel oil, and paraffin "wax." Other than combustion, alkanes undergo few reactions. In fact, when a molecule contains an alkane portion and a nonalkane portion, we often ignore the presence of the alkane portion because it is relatively unreactive. Alkanes undergo few reactions because they have no **functional group**, where reactions usually occur. Functional groups are reactive parts such as double bonds, hydroxyl groups, or halogen atoms. Most organic compounds are characterized and classified by the functional groups they contain.

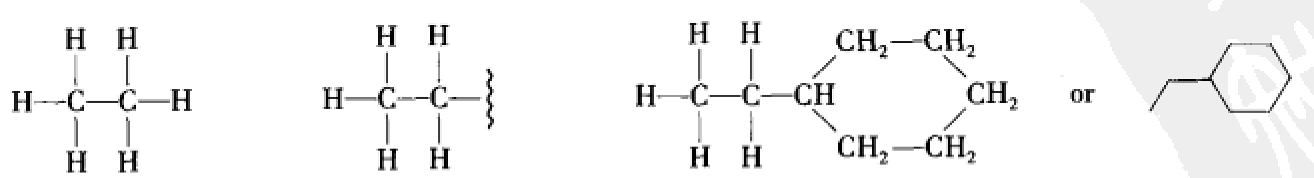
The **cycloalkanes** are a special class of alkanes that are in the form of a ring. Figure 3-1 shows some cycloalkanes. Simple cycloalkanes are rings of CH_2 groups (methylene groups). Each one has exactly twice as many hydrogen atoms as carbon atoms, giving the general molecular formula C_nH_{2n}. This general formula has two fewer hydrogen atoms than the $(2n + 2)$ formula for an acyclic alkane because a ring has no ends, and no hydrogens are needed to cap off the ends of the chain.



cyclopropane (环丙烷) C_3H_6　cyclobutane (环丁烷) C_4H_8　cyclopentane (环戊烷) C_5H_{10}　cyclohexane (环己烷) C_6H_{12}　cycloheptane (环庚烷) C_7H_{14}

Figure 3-1 Structures of some cycloalkanes.

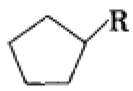
A molecule with a functional group may be represented as the functional group with **alkyl groups** attached. An **alkyl group** is an alkane portion of a molecule, with one hydrogen atom removed to allow bonding to the functional group. Figure 3-2 shows how an alkyl group is named, using a substituted cycloalkane as the example.



ethane　ethyl group (乙基)　ethylcyclohexane (乙基环己烷)　ethylcyclohexane

Figure 3-2 Naming of alkyl groups. Alkyl groups are named like the alkanes they are derived from, with a *-yl* suffix.

We are often concerned with the structure of only the most important part of a molecule. In these cases, we often use the symbol R as a substituent. The R group is simply an alkyl group. We presume that the exact nature of the R group is not important.

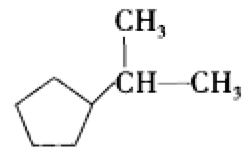


an alkylcyclopentane
(烷基环戊烷)

might be

methylcyclopentane
(甲基环戊烷)

or

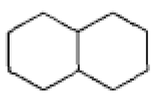


isopropylcyclopentane
(异丙基环戊烷)

or other compounds

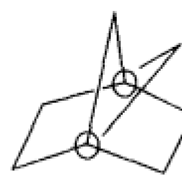
Bicyclic alkanes Two or more rings can be joined into *bicyclic* or *polycyclic* systems. There are three ways that two rings may be joined. **Fused rings** are most common, sharing two adjacent carbon atoms and the bond between them. **Bridged rings** are also common, sharing two nonadjacent carbon atoms (the **bridgehead carbons**) and one or more carbon atoms (the bridge) between them. **Spirocyclic compounds**, in which the two rings share only one carbon atom, are relatively rare.

fused bicyclic (稠二环)



bicyclo[4. 4. 0]decane (双环[4. 4. 0]癸烷)
(decalin, 十氢化萘)

bridged bicyclic(桥二环)



bicyclo[2. 2. 1]heptane (双环[2. 2. 1]庚烷)
(norbornane, 降冰片烷)

spirocyclic(螺环)

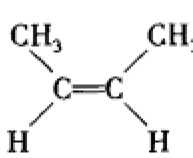
spiro[4. 4]nonane
(螺环[4. 4]壬烷)

3-1B Alkenes

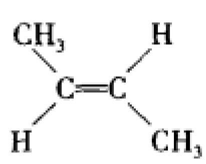
Alkenes are hydrocarbons that contain carbon -carbon double bonds. A carbon-carbon double bond is the most reactive part of an alkene, so we say that the double bond is the *functional group* of the alkene. Alkene names end in the *-ene* suffix, as shown by the following examples:

$CH_2{=}CH_2$	$CH_2{=}CH{-}CH_3$	$CH_2{=}CH{-}CH_2{-}CH_3$	$CH_3{-}CH{=}CH{-}CH_3$
ethene (ethylene, 乙烯)	propene (propylene, 丙烯)	1-butene (1-丁烯)	2-butene (2-丁烯)

Carbon-carbon double bonds cannot rotate, and many alkenes show geometric (cis-trans) isomerism. The following are the cis-trans isomers of some simple alkenes:



cis-2-butene
(顺-2-丁烯)

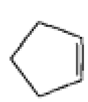


trans-2-butene
(反-2-丁烯)

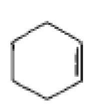
cis-2-hexene
(顺-2-己烯)

trans-2-hexene
(反-2-己烯)

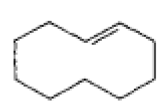
Cycloalkenes are also common. Unless the rings are very large, cycloalkenes are always the cis isomers, and the term *cis* is omitted from the names. In a large ring, a trans double bond may occur, giving a *trans*-cycloalkene.



cyclopentene
(环戊烯)



cyclohexene
(环己烯)



trans-cyclodecene
(反-环癸烯)

3-1C Alkynes

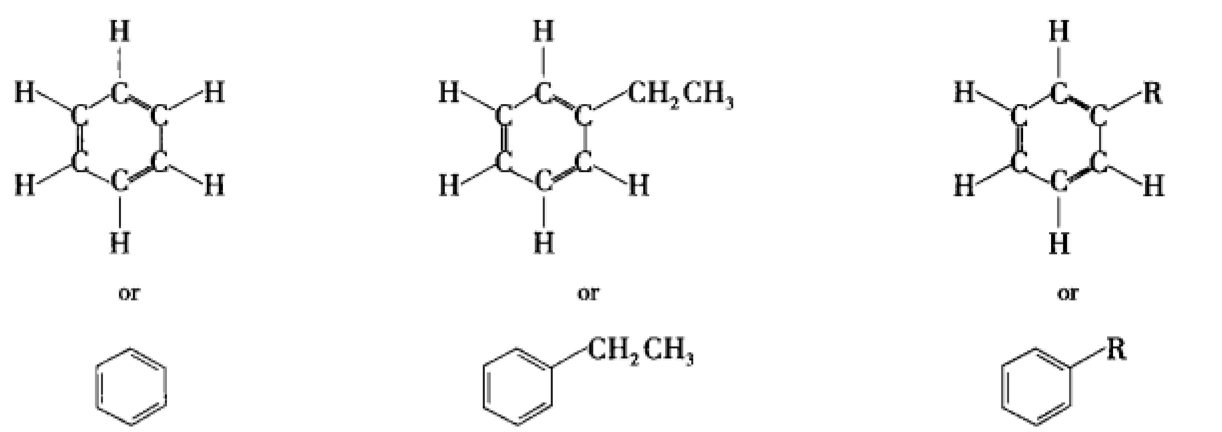
Alkynes are hydrocarbons with carbon-carbon triple bonds as their functional group. Alkyne names generally have the *-yne* suffix, although some of their common names (*acetylene*, for example) do not conform to this rule. The triple bond is linear, so there is no possibility of geometric (cis-trans) isomerism in alkynes.

$H-C\equiv C-H$	$H-C\equiv C-CH_3$	$H-C\equiv C-CH_2-CH_3$	$CH_3-C\equiv C-CH_3$
ethyne (acetylene, 乙炔)	propyne (methylacetylene, 丙炔)	1-butyne (1-丁炔)	2-butyne (2-丁炔)

In an alkyne, four atoms must be in a straight line. These four collinear atoms are not easily bent into a ring, so cycloalkynes are rare. Cycloalkynes are stable only if the ring is large.

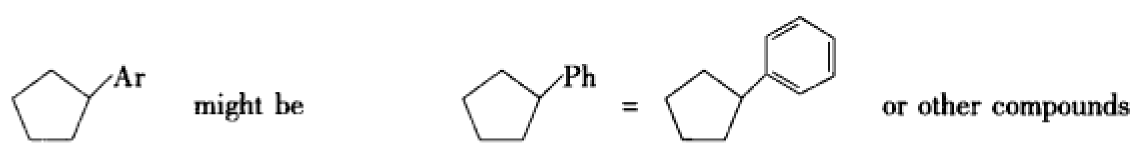
3-1D Aromatic Hydrocarbons

The following compounds may look like cycloalkenes, but their properties are different from those of simple alkenes. These **aromatic hydrocarbons** (also called **arenes**) are all derivatives of *benzene*, represented by a six-membered ring with three double bonds. This bonding arrangement is particularly stable, for reasons that are explained in Chapter 17.



benzene (苯) ethylbenzene (乙基苯) an alkylbenzene (烷基苯)

Just as a generic alkyl group substituent is represented by R, a generic aryl group is represented by Ar. When a benzene ring serves as a substituent, it is called a phenyl group, abbreviated Ph.



an arylcyclopentane (芳基环戊烷) phenylcyclopentane (苯基环戊烷)

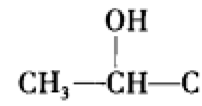
3-2 Organic Compounds Containing Oxygen

Many organic compounds contain oxygen atoms bonded to alkyl groups. The major classes of oxygen-containing compounds are alcohols, ethers, ketones, aldehydes, carboxylic acids, and acid derivatives.

3-2A Alcohols

Alcohols are organic compounds that contain the **hydroxyl group** (—OH) as their functional group. The general formula for an alcohol is R—OH. Alcohols are among the most polar organic compounds because the hydroxyl group is strongly polar and can participate in hydrogen bonding. Some of the simple alcohols like ethanol and methanol are miscible (soluble in all proportions) with water. Names of alcohols end in the *-ol* suffix from the

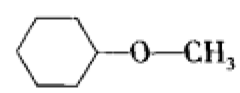
word "alcohol," as shown for the following common alcohols:

R—OH	CH_3—OH	CH_3CH_2—OH	CH_3—CH_2—CH_2—OH	
an alcohol (醇)	methanol (甲醇) (methyl alcohol)	ethanol (乙醇) (ethyl alcohol)	1-propanol (1-丙醇) (*n*-propyl alcohol)	2-propanol (2-丙醇) (isopropyl alcohol)

Alcohols are some of the most common organic compounds. Methyl alcohol (methanol), also known as "wood alcohol," is used as an industrial solvent and as an automobile racing fuel. Ethyl alcohol (ethanol) is sometimes called "grain alcohol" because it is produced by the fermentation of grain or almost any other organic material. "Isopropyl alcohol" is the common name for 2-propanol, used as "rubbing alcohol."

3-2B Ethers

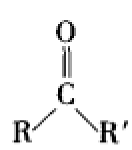
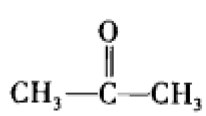
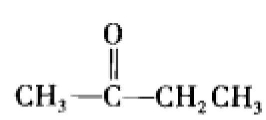
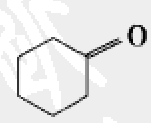
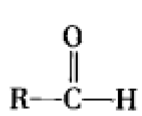
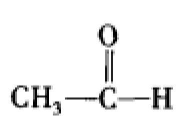
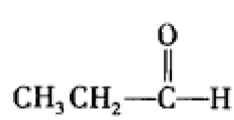
Ethers are composed of two alkyl groups bonded to an oxygen atom. The general formula for an ether is R—O—R′. (The symbol R′ represents another alkyl group, either the same as or different from the first.) Like alcohols, ethers are much more polar than hydrocarbons. Ethers have no O—H hydrogens, however, so they cannot hydrogen bond with themselves. Ether names are often formed from the names of the alkyl groups and the word "ether." Diethyl ether is the common "ether" used for starting engines in cold weather and once used for surgical anesthesia.

R—O—R′	CH_3—O—CH_3	CH_3CH_2—O—CH_2CH_3	
ROR′, an ether (醚)	dimethyl ether (甲醚)	diethyl ether (乙醚)	cyclohexyl methyl ether (甲基环己基醚)

3-2C Aldehydes and Ketones

The **carbonyl group**, C=O, is the functional group for both aldehydes and ketones. A **ketone** has two alkyl groups bonded to the carbonyl group; an **aldehyde** has one alkyl group and a hydrogen atom bonded to the carbonyl group. Ketone names generally have the *-one* suffix; aldehyde names use either the *-al* suffix or the *-aldehyde* suffix.

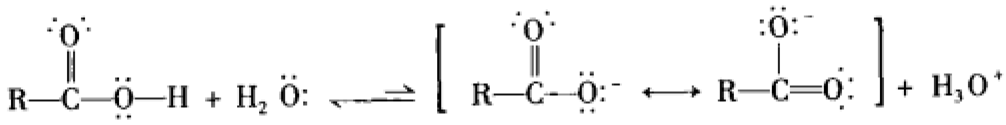
The carbonyl group is strongly polar, and most ketones and aldehydes are somewhat soluble in water. Both acetone and acetaldehyde are miscible with water. Acetone, often used as nail polish remover, is a common solvent with low toxicity.

			
RCOR′, a ketone (酮)	2-propanone (acetone) (丙酮)	2-butanone (methyl ethyl ketone) (2-丁酮, 甲基乙基酮)	cyclohexanone (环己酮)
			
or RCHO an aldehyde (醛)	or CH_3CHO ethanal (acetaldehyde) (乙醛)	or CH_3CH_2CHO propanal (propionaldehyde) (丙醛)	or $CH_3CH_2CH_2CHO$ butanal (butyraldehyde) (丁醛)

3-2D Carboxylic Acids

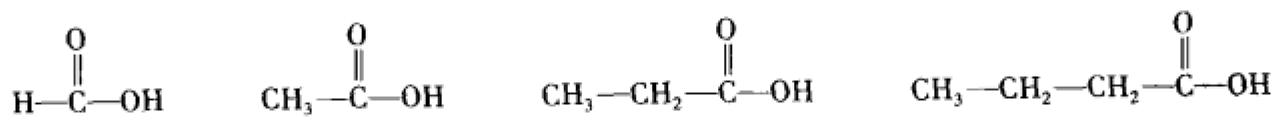
Carboxylic acids contain the **carboxyl group**, —COOH, as their functional group. The general formula for a

carboxylic acid is R—COOH (*or* RCO_2H). The carboxyl group is a combination of a carbonyl group and a hydroxyl group, but this combination has different properties from those of ketones and alcohols. Carboxylic acids owe their acidity (pK_a of about 5) to the resonance-stabilized *carboxylate anions* formed by deprotonation. The following reaction shows the dissociation of a carboxylic acid:



carboxylic acid (羧酸) carboxylate anion (羧酸根离子)

Systematic names for carboxylic acids use the *-oic acid* suffix, but historical names are commonly used. Formic acid was first isolated from ants, genus *Formica*. Acetic acid, found in vinegar, gets its name from the Latin word for "sour" (*acetum*). Propionic acid gives the tangy flavor to sharp cheeses, and butyric acid provides the pungent aroma of rancid butter.



methanoic acid	ethanoic acid	propanoic acid	butanoic acid
(formic acid)	(acetic acid)	(propionic acid)	(butyric acid)
(甲酸)	(乙酸)	(丙酸)	(丁酸)

Carboxylic acids are strongly polar, like ketones, aldehydes, and alcohols. They are relatively soluble in water; in fact, all four of the carboxylic acids shown here are miscible (soluble in all proportions) with water.

3-2E Carboxylic Acid Derivatives

Several related functional groups can be formed from carboxylic acids. In such **acid derivatives**, the —OH group of a carboxylic acid is replaced by other electron-withdrawing groups. Among these functional groups are **acid chlorides**, **esters**, and **amides**. In acid chlorides, the hydroxyl group of the acid is replaced by a chlorine atom. In esters, the hydroxyl group is replaced by an alkoxyl (—O—R) group. And in amides, the hydroxyl group is replaced by an amino ($—NH_2$) group. All of these groups can be converted back to carboxylic acids by acidic or basic hydrolysis.

or R—COOH	or R—COCl	or R—COOR′	or R—$CONH_2$
carboxylic acid (羧酸)	acid chloride (酰氯)	ester (酯)	amide (酰胺)

or CH_3COOH	or CH_3COCl	or $CH_3COOCH_2CH_3$	or CH_3CONH_2
acetic acid (乙酸)	acetyl chloride (乙酰氯)	ethyl acetate (乙酸乙酯)	acetamide (乙酰胺)

3-3 Organic Compounds Containing Nitrogen

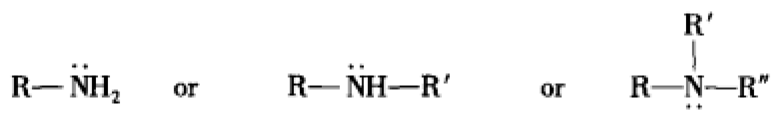
Nitrogen is another element often found in the functional groups of organic compounds. The most common "nitrogenous" organic compounds are amines, amides, and nitriles.

3-3A Amines

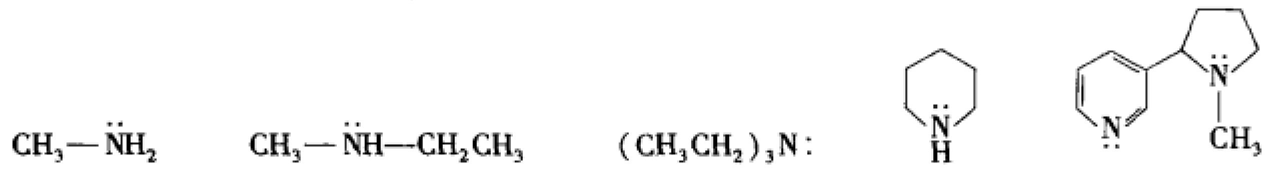
Amines are alkylated derivatives of ammonia. Like ammonia, amines are basic.

$$R—\ddot{N}H_2 + H_2O \rightleftharpoons R—\overset{+}{N}H_3 \quad {}^-OH \quad K_b \approx 10^{-3}$$

Because of their basicity ("alkalinity"), naturally occurring amines are often called *alkaloids*. Simple amines are named by naming the alkyl groups bonded to nitrogen and adding the word "amine." The structures of some simple amines are shown below, together with the structure of nicotine, a toxic alkaloid found in tobacco leaves.



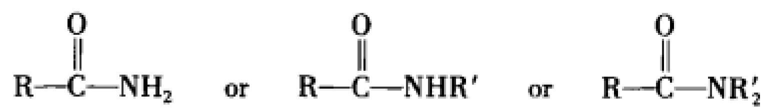
amines (胺)



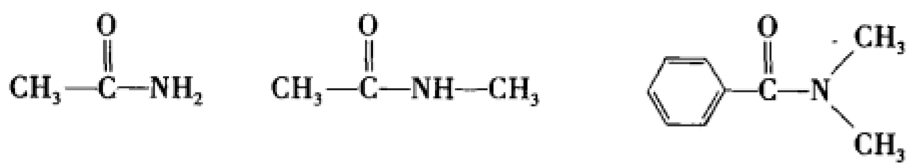
methylamine (甲胺) ethylmethylamine (甲基乙基胺) triethylamine (三乙胺) piperidine (哌啶) nicotine (尼古丁)

3-3B Amides

Amides are acid derivatives that resulf from a combination of an acid with ammonia or an amine. Proteins have the structure of long-chain, complex amides.

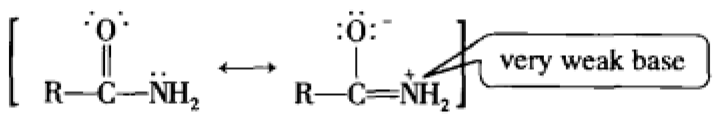


amides (酰胺)



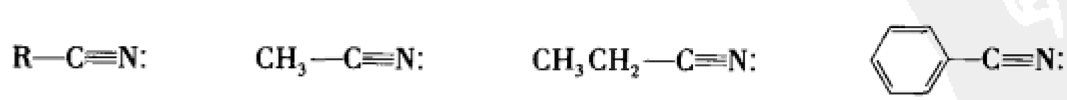
acetamide (乙酰胺) *N*-methylacetamide (*N*-甲基乙酰胺) *N*,*N*-dimethylbenzamide (*N*,*N*-二甲基苯甲酰胺)

Amides are among the most stable acid derivatives. The nitrogen atom of an amide is not as basic as the nitrogen of an amine because of the electron-withdrawing effect of the carbonyl group. The following resonance forms help to show why amides are very weak bases:



3-3C Nitriles

A **nitrile** is a compound containing the **cyano group**, —C≡N.



a nitrile (腈) acetonitrile (乙腈) propionitrile (丙腈) benzonitrile (苯基腈)

All of these classes of compounds are summarized in the table of Common Organic Compounds and Functional Groups, given on the front inside cover for convenient reference.

3-4 Nomenclature of Alkanes

The names *methane*, *ethane*, *propane*, and *butane* have historical roots. From pentane on, alkanes are named

using the Greek word for the number of carbon atoms, plus the suffix *-ane* to identify the molecule as an alkane. Table 3-2 gives the names and physical properties of the *n*-alkanes up to 20 carbon atoms. Any isomers of these compounds have the same molecular formulas even though their structures are different. Notice how the molecular formulas increase by two hydrogen atoms each time a carbon atom is added.

The structures of the alkanes in Table 3-2 are purposely written as chains of $—CH_2—$ groups (**methylene groups**), terminated at each end by a hydrogen atom. This is the general formula for the unbranched (straight-chain) alkanes. These alkanes differ only by the number of methylene groups in the chain. If the molecule contains n carbon atoms, it must contain $(2n + 2)$ hydrogen atoms, giving the general molecular formula C_nH_{2n+2}.

TABLE 3-2 Names and Formulas of the Unbranched Alkanes, Called the *n*-Alkanes

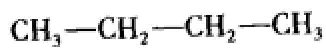
Alkane	Number of Carbons	Structure	Formula
methane (甲烷)	1	$H—CH_2—H$	CH_4
ethane (乙烷)	2	$H—(CH_2)_2—H$	C_2H_6
propane (丙烷)	3	$H—(CH_2)_3—H$	C_3H_8
butane (丁烷)	4	$H—(CH_2)_4—H$	C_4H_{10}
pentane (戊烷)	5	$H—(CH_2)_5—H$	C_5H_{12}
hexane (己烷)	6	$H—(CH_2)_6—H$	C_6H_{14}
heptane (庚烷)	7	$H—(CH_2)_7—H$	C_7H_{16}
octane (辛烷)	8	$H—(CH_2)_8—H$	C_8H_{18}
nonane (壬烷)	9	$H—(CH_2)_9—H$	C_9H_{20}
decane (癸烷)	10	$H—(CH_2)_{10}—H$	$C_{10}H_{22}$
undecane (十一烷)	11	$H—(CH_2)_{11}—H$	$C_{11}H_{24}$
dodecane (十二烷)	12	$H—(CH_2)_{12}—H$	$C_{12}H_{26}$
tridecane (十三烷)	13	$H—(CH_2)_{13}—H$	$C_{13}H_{28}$
tetradecane (十四烷)	14	$H—(CH_2)_{14}—H$	$C_{14}H_{30}$
pentadecane (十五烷)	15	$H—(CH_2)_{15}—H$	$C_{15}H_{32}$
hexadecane (十六烷)	16	$H—(CH_2)_{16}—H$	$C_{16}H_{34}$
heptadecane (十七烷)	17	$H—(CH_2)_{17}—H$	$C_{17}H_{36}$
octadecane (十八烷)	18	$H—(CH_2)_{18}—H$	$C_{18}H_{38}$
nonadecane (十九烷)	19	$H—(CH_2)_{19}—H$	$C_{19}H_{40}$
eicosane (二十烷)	20	$H—(CH_2)_{20}—H$	$C_{20}H_{42}$
triacontane (三十烷)	30	$H—(CH_2)_{30}—H$	$C_{30}H_{62}$

A series of compounds, like the *n*-alkanes, that differ only by the number of $—CH_2—$ groups, is called a *homologous series*, and the individual members of the series are called **homologs**. For example, butane is a homolog of propane, and both of these are homologs of hexane and decane.

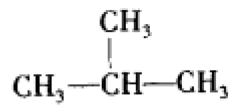
Although we have derived the C_nH_{2n+2} formula using the unbranched *n*-alkanes, it applies to branched alkanes as well. Any isomer of one of these *n*-alkanes has the same molecular formula. Just as butane and pentane follow the C_nH_{2n+2} rule, their branched isomers isobutane, isopentane, and neopentane also follow the rule.

3-4A Common Names

If all alkanes had unbranched (straight-chain) structures, their nomenclature would be simple. Most alkanes have structural isomers, however, and we need a way of naming all the different isomers. For example, there are two isomers of formula C_4H_{10}. The unbranched isomer is simply called *butane* (or *n-butane*, meaning "normal" butane), and the branched isomer is called *isobutane*, meaning an "isomer of butane."

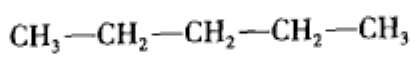


butane (*n*-butane)
[(正)丁烷]

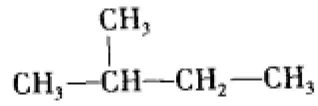


isobutane
(异丁烷)

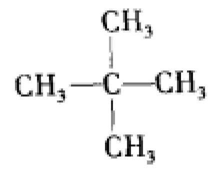
The three isomers of C_5H_{12} are called *pentane* (or *n-pentane*), *isopentane*, and *neopentane.*



pentane (*n*-pentane)
[(正)戊烷]



isopentane
(异戊烷)



neopentane
(新戊烷)

Isobutane, *isopentane*, and *neopentane* are **common names** or **trivial names**, meaning historical names arising from common usage. Common names cannot easily describe the larger, more complicated molecules having many isomers, however. The number of isomers for any molecular formula grows rapidly as the number of carbon atoms increases. For example, there are 5 structural isomers of hexane, 18 isomers of octane, and 75 isomers of decane! We need a system of nomenclature that enables us to name complicated molecules without having to memorize hundreds of these historical common names.

3-4B IUPAC or Systematic Names

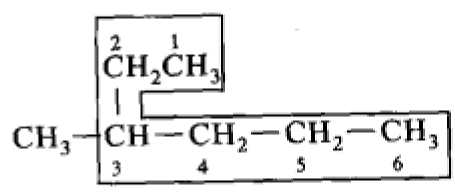
A group of chemists representing the countries of the world met in 1892 to devise a system for naming compounds that would be simple to use, require a minimum of memorization, and yet be flexible enough to name even the most complicated organic compounds. This was the first meeting of the group that came to be known as the International Union of Pure and Applied Chemistry, abbreviated **IUPAC**. This international group has developed a detailed system of nomenclature that we call the **IUPAC rules**. The IUPAC rules are accepted throughout the world as the standard method for naming organic compounds. The names that are generated using this system are called **IUPAC names** or **systematic names**.

The IUPAC system works consistently to name many different families of compounds. We will consider the naming of alkanes in detail, and later extend these rules to other kinds of compounds as we encounter them. The IUPAC system uses the longest chain of carbon atoms as the main chain, which is numbered to give the locations of side chains. Four rules govern this process.

Rule 1: The Main Chain The first rule of nomenclature gives the base name of the compound.

Find the longest continuous chain of carbon atoms, and use the name of this chain as the base name of the compound.

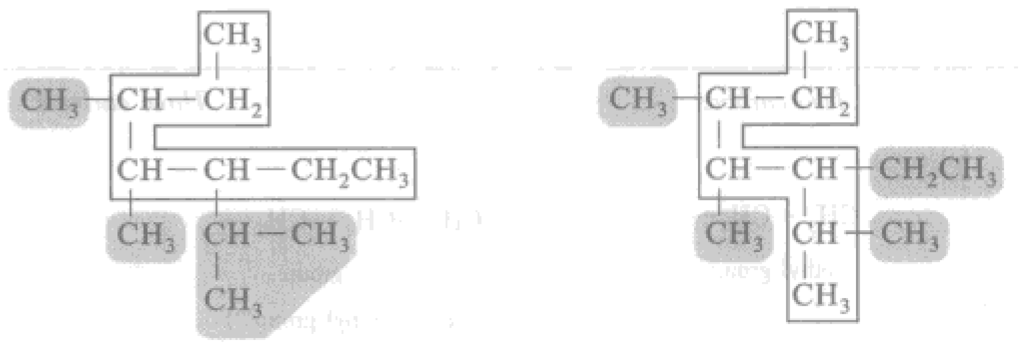
For example, the longest chain of carbon atoms in the compound below contains six carbons, so the compound is named as a *hexane* derivative. The longest chain is rarely drawn in a straight line; look carefully to find it.



3-methylhexane
(3-甲基己烷)

The groups attached to the main chain are called **substituents** because they are substituted (in place of a hydrogen atom) on the main chain. *When there are two longest chains of equal length, use the chain with the*

greater number of substituents as the main chain. The following compound contains two different seven-carbon chains and is named as a *heptane*. We choose the chain on the right as the main chain because it has more substituents attached to the chain.



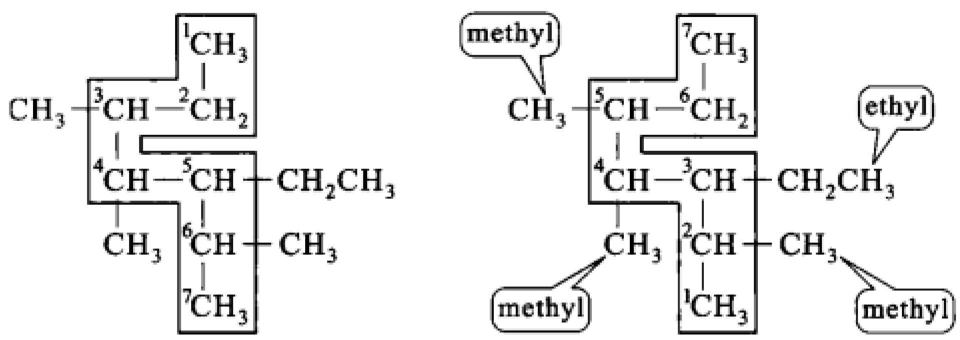
wrong — seven-carbon chain, but only three substituents (取代基)

correct — seven-carbon chain, four substituents

Rule 2: Numbering the Main Chain To give the locations of the substituents, assign a number to each carbon atom on the main chain.

Number the longest chain, beginning with the end of the chain nearest a substituent.

We start the numbering from the end nearest a branch so the numbers of the substituted carbons will be as low as possible. In the preceding heptane structure on the right, numbering from top to bottom gives the first branch at C3 (carbon atom 3), but numbering from bottom to top gives the first branch at C2. Numbering from bottom to top is correct. (If each end had a substituent the same distance in, we would start at the end nearer the second branch point.)



incorrect

correct

3-ethyl-2,4,5-trimethylheptane(2,4,5−三甲基−3−乙基庚烷)

Rule 3: Naming Alkyl Groups Next, name the substituent groups.

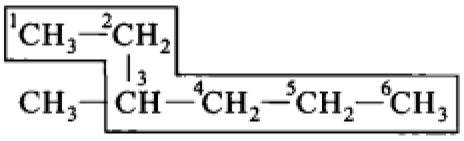
Name the substituent groups attached to the longest chain as **alkyl groups**.

Give the location of each alkyl group by the number of the main-chain carbon atom to which it is attached.

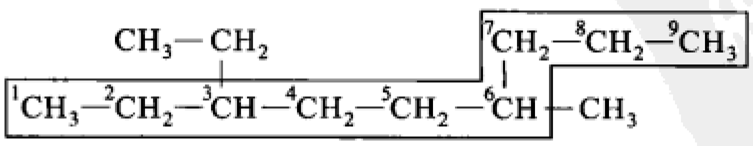
Alkyl groups are named by replacing the *-ane* suffix of the alkane name with *-yl*. *Methane* becomes *methyl*; *ethane* becomes *ethyl*.

CH_4	methane	$CH_3—$	methyl group (甲基)
$CH_3—CH_3$	ethane	$CH_3—CH_2—$	ethyl group (乙基)
$CH_3—CH_2—CH_3$	propane	$CH_3—CH_2—CH_2—$	propyl group (丙基)

The following alkanes show the use of alkyl group nomenclature.



3-methylhexane



3-ethyl-6-methylnonane (6−甲基−3−乙基壬烷)

Figure 3−3 gives the names of the most common alkyl groups, those having up to four carbon atoms. The *propyl and butyl* groups are simply unbranched three-and four-carbon alkyl groups. These groups are often named as "*n*-propyl" and "*n*-butyl" groups, to distinguish them from other kinds of (branched) propyl and butyl groups.

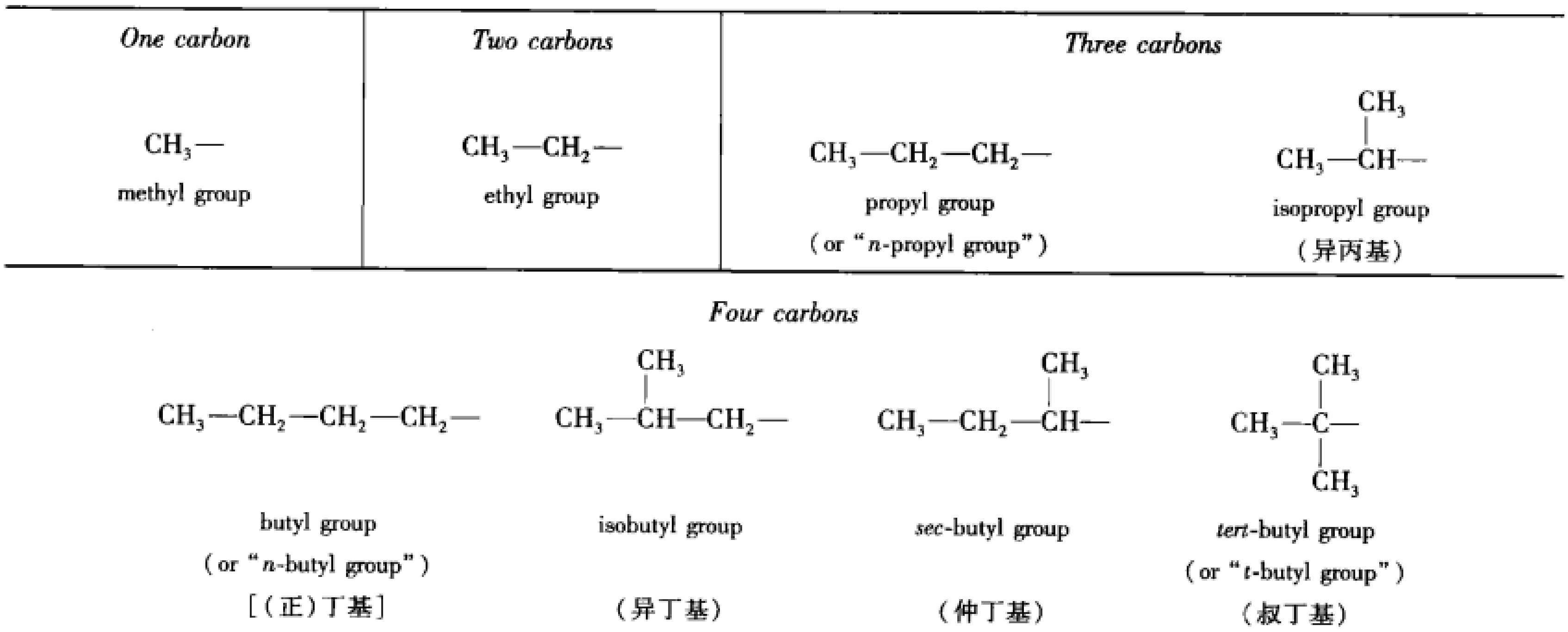
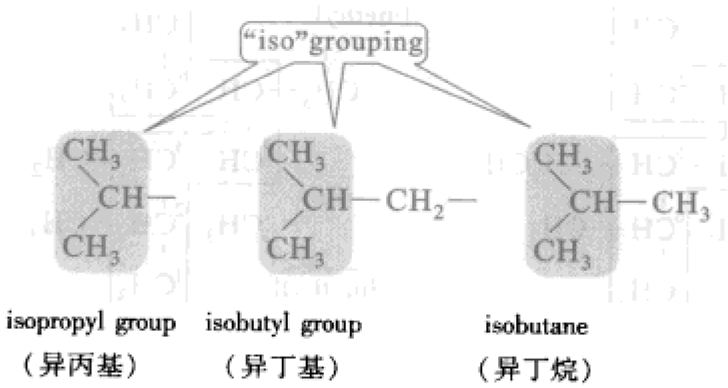
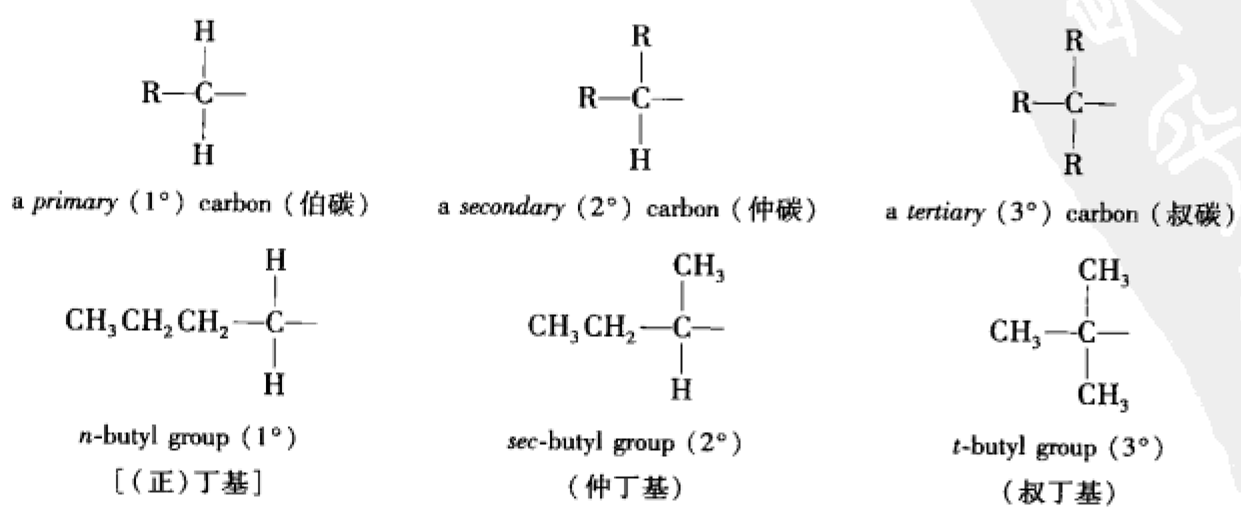


Figure 3−3 Some common alkyl groups.

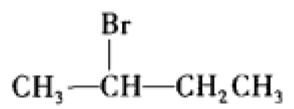
The simple branched alkyl groups are usually known by common names. The isopropyl and isobutyl groups have a characteristic "iso" $(CH_3)_2CH$ grouping, just as in isobutane.

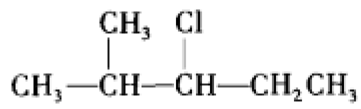


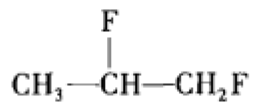
The names of the *secondary*-butyl (*sec*-butyl) and *tertiary*-butyl (*tert*-butyl or *t*-butyl) groups are based on the **degree of alkyl substitution** of the carbon atom attached to the main chain. In the *sec*-butyl group, the carbon atom bonded to the main chain is **secondary** (2°), or bonded to two other carbon atoms. In the *t*-butyl group, it is **tertiary** (3°), or bonded to three other carbon atoms. In both the *n*-butyl group and the isobutyl group, the carbon atoms bonded to the main chain are **primary** (1°), bonded to only one other carbon atom.



Haloalkanes can be named just like alkanes, with the halogen atom treated as a substituent. Halogen substituents are named *fluoro-*, *chloro-*, *bromo-*, and *iodo-*.

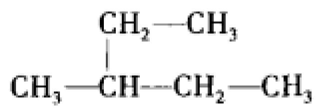

2-bromobutane
(2-溴丁烷)

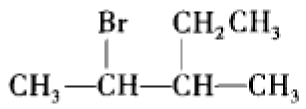

3-chloro-2-methylpentane
(2-甲基-3-氯戊烷)

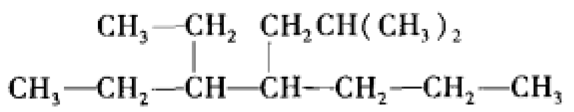

1,2-difluoropropane
(1,2-二氟丙烷)

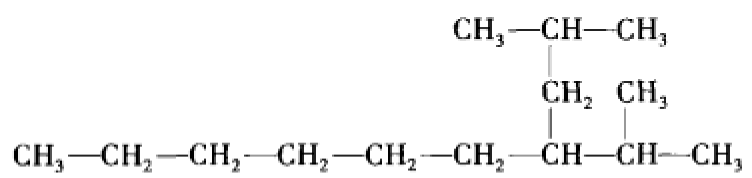
PROBLEM 3-1

Name the following alkanes and haloalkanes.

(a) 

(b) 

(c) 

(d) 

Rule 4: Organizing Multiple Groups The final rule deals with naming compounds with more than one substituent.

When two or more substituents are present, list them in alphabetical order.

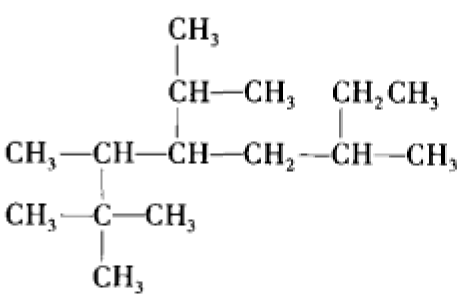
When two or more of the *same* alkyl substituent are present, use the prefixes *di-*, *tri-*, *tetra-*, etc. to avoid having to name the alkyl group twice.

di-means 2 *tri*-means 3 *tetra*-means 4 *penta*-means 5 *hexa*-means 6

When substituents are alphabetized, *iso*-is used as part of the alkyl group name, but the hyphenated prefixes are not. Thus *isobutyl* is alphabetized with *i*, but *n*-butyl, *t*-butyl, and *sec*-butyl are alphabetized with *b*. The number prefixes *di-*, *tri-*, *tetra-*, etc. are ignored in alphabetizing.

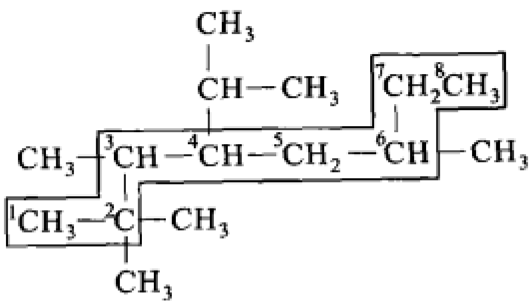
SOLVED PROBLEM 3-1

Give a systematic (IUPAC) name for the following compound.



SOLUTION

The longest carbon chain contains eight carbon atoms, so this compound is named as an octane. Numbering from left to right gives the first branch on C2; numbering from right to left gives the first branch on C3, so we number from left to right.



There are four methyl groups: two on C2, one on C3, and one on C6. These four groups will be listed as "2,2,3,6-tetramethyl…" There is an isopropyl group on C4. Listing the isopropyl group and the methyl groups alphabetically, we have

4-isopropyl-2,2,3,6-tetramethyloctane
(2,2,3,6-四甲基-4-异丙基辛烷)

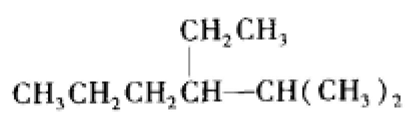
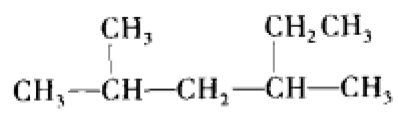
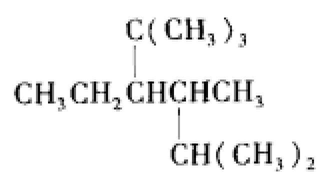
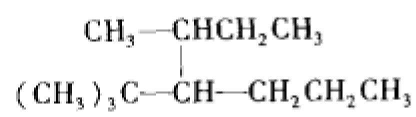
PROBLEM 3-2

Write structures for the following compounds.

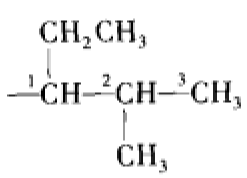
(a) 3-ethyl-3-methylpentane
(b) 3-methyl-5-propylnonane
(c) 4-*t*-butyl-2-methylheptane
(d) 5-isopropyl-3,3,4-trimethyloctane

PROBLEM 3-3

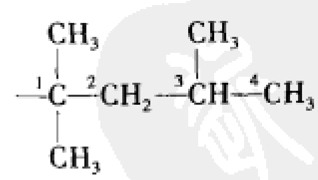
Provide IUPAC names for the following compounds.

(a) $(CH_3)_2CHCH_2CH_3$
(b) $CH_3-C(CH_3)_2-CH_3$
(c) 
(d) 
(e) 
(f) 

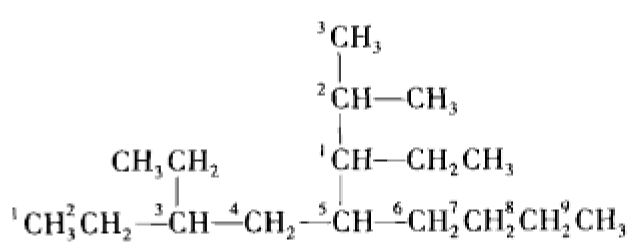
Complex Substituents Complex alkyl groups are named by a systematic method using the longest alkyl chain as the base alkyl group. The base alkyl group is numbered beginning with the carbon atom (the "head carbon") bonded to the main chain. The substituents on the base alkyl group are listed with appropriate numbers, and parentheses are used to set off the name of the complex alkyl group. The following examples illustrate the systematic method for naming complex alkyl groups.



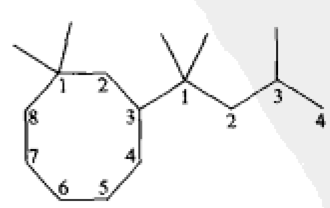
a (1-ethyl-2-methylpropyl) group
(2-甲基-1-乙基丙基)



a (1,1,3-trimethylbutyl) group
(1,1,3-三甲基丁基)



3-ethyl-5-(1-ethyl-2-methylpropyl) nonane
[3-乙基-5-(2-甲基-1-乙基丙基)壬烷]



1,1-dimethyl-3-(1,1,3-trimethylbutyl) cyclooctane
[1,1-二甲基-3-(1,1,3-三甲基丁基)环辛烷]

PROBLEM 3-4

Draw the structures of the following groups, and give their more common names.

(**a**) the (1-methylethyl) group (**b**) the (2-methylpropyl) group

(**c**) the (1-methylpropyl) group (**d**) the (1,1-dimethylethyl) group

PROBLEM 3-5

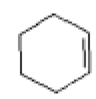
Draw the structures of the following compounds.

(**a**) 4-(1-methylethyl)heptane (**b**) 5-(1,2,2-trimethylpropyl)nonane

3-5 Nomenclature of Alkenes

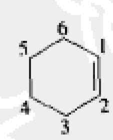
3-5A IUPAC and Common Names of Alkenes

Simple alkenes are named much like alkanes, using the root name of the longest chain containing the double bond. The ending is changed from *-ane* to *-ene*. For example, "ethane" becomes "ethene," "propane" becomes "propene," and "cyclohexane" becomes "cyclohexene."

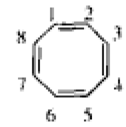
	$CH_2{=}CH_2$	$CH_2{=}CH{-}CH_3$	
IUPAC names:	ethene (乙烯)	propene (丙烯)	cyclohexene (环己烯)
Common names:	ethylene	propylene	

When the chain contains more than three carbon atoms, a number is used to give the location of the double bond. The chain is numbered starting from the end closest to the double bond, and the double bond is given the *lower* number of its two double-bonded carbon atoms. Cycloalkenes are assumed to have the double bond in the number 1 position.

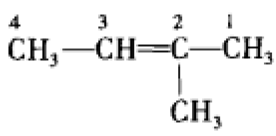
In 1993, the IUPAC recommended a logical change in the positions of the numbers used in names. Instead of placing the numbers before the root name (1-utene), they recommended placing them immediately before the part of the name they locate (but-1-ene). You should be prepared to recognize names using either placement of the numbers, because both are widely used. In this section, names using the new number placement are printed in green. Throughout this book, we will use the new number placement whenever it helps to clarify a name.

	$\overset{1}{C}H_2{=}\overset{2}{C}H{-}\overset{3}{C}H_2{-}\overset{4}{C}H_3$	$\overset{1}{C}H_2{=}\overset{2}{C}H{-}\overset{3}{C}H_2{-}\overset{4}{C}H_2{-}\overset{5}{C}H_3$	
IUPAC names:	1-butene (1-丁烯)	1-pentene (1-戊烯)	cyclohexene
new IUPAC names:	but-1-ene	pent-1-ene	
	$\overset{1}{C}H_3{-}\overset{2}{C}H{=}\overset{3}{C}H{-}\overset{4}{C}H_3$	$\overset{1}{C}H_3{-}\overset{2}{C}H{=}\overset{3}{C}H{-}\overset{4}{C}H_2{-}\overset{5}{C}H_3$	
IUPAC names:	2-butene	2-pentene	
new IUPAC names:	but-2-ene	pent-2-ene	

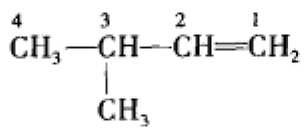
A compound with two double bonds is a **diene**. A **triene** has three double bonds, and a **tetraene** has four. Numbers are used to specify the locations of the double bonds.

	$\overset{1}{C}H_2{=}\overset{2}{C}H{-}\overset{3}{C}H{=}\overset{4}{C}H_2$	$\overset{7}{C}H_3{-}\overset{6}{C}H{=}\overset{5}{C}H{-}\overset{4}{C}H{=}\overset{3}{C}H{-}\overset{2}{C}H{=}\overset{1}{C}H_2$	
IUPAC names:	1,3-butadiene (1,3-丁二烯)	1,3,5-heptatriene (1,3,5-庚三烯)	1,3,5,7-cyclooctatetraene
new IUPAC names:	buta-1,3-diene	hepta-1,3,5-triene	cycloocta-1,3,5,7-tetraene (1,3,5,7-环辛四烯)

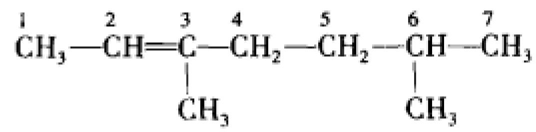
Each alkyl group attached to the main chain is listed with a number to give its location. Note that the double bond is still given preference in numbering, however.



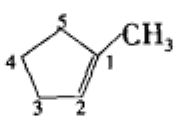
2-methyl-2-butene
2-methylbut-2-ene
(2-甲基-2-丁烯)



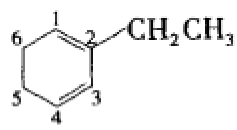
3-methyl-1-butene
3-methylbut-1-ene
(3-甲基-1-丁烯)



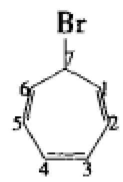
3,6-dimethyl-2-heptene
3,6-dimethylhept-2-ene
(3,6-二甲基-2-庚烯)



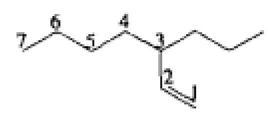
1-methylcyclopentene
(1-甲基环戊烯)



2-ethyl-1,3-cyclohexadiene
2-ethylcyclohexa-1,3-diene
(2-乙基-1,3-环乙二烯)



7-bromo-1,3,5-cycloheptatriene
7-bromocyclohepta-1,3,5-triene
(7-溴-1,3,5-环庚三烯)



3-propyl-1-heptene
3-propylhept-1-ene
(3-丙基-1-庚烯)

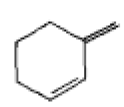
Alkenes as Substituents Alkenes named as substituents are called *alkenyl groups*. They can be named systematically (ethenyl, propenyl, etc.), or by common names. Common alkenyl substituents are the vinyl, allyl, methylene, and phenyl groups. The phenyl group (Ph) is different from the others because it is aromatic (see Chapter 17) and does not undergo the typical reactions of alkenes.

$\}{=}CH_2$

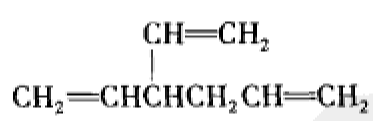
methylene group (亚甲基)
(methylidene group)

$\}{-}CH{=}CH_2$

vinyl group (乙烯基)
(ethenyl group)



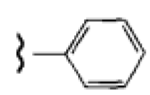
3-methylenecyclohexene
(3-亚甲基环己烯)



3-vinyl-1,5-hexadiene
3-vinylhexa-1,5-diene
(3-乙烯基-1,5-己二烯)

$\}{-}CH_2{-}CH{=}CH_2$

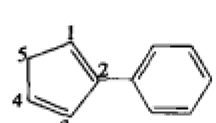
allyl group (烯丙基)
(2-propenyl group)



phenyl group (苯基)
(Ph)

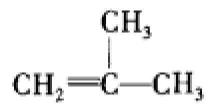
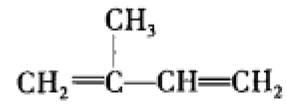
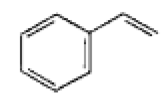
$CH_2{=}CH{-}CH_2{-}Cl$

allyl chloride
(3-chloropropene)
(烯丙基氯,3-氯代丙烯)



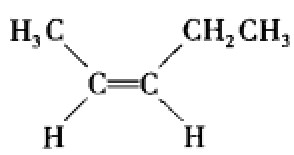
2-phenyl-1,3-cyclopentadiene
2-phenylcyclopenta-1,3-diene
(2-苯基-1,3-环戊二烯)

Common Names Most alkenes are conveniently named by the IUPAC system, but common names are sometimes used for the simplest compounds.

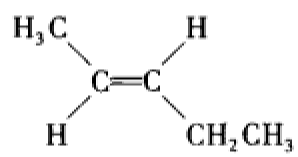
					
IUPAC names:	ethene	propene	2-methylpropene	2-methylbuta-1,3-diene	ethenylbenzene
common name:	ethylene	propylene	isobutylene	isoprene	styrene
			(2-甲基丙烯,异丁烯)	(2-甲基-1,3-丁二烯,异戊二烯)	(乙烯基苯,苯乙烯)

3-5B Cis-Trans Nomenclature

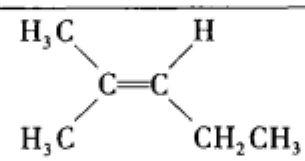
In Chapter 2, we saw how the rigidity and lack of rotation of carbon-carbon double bonds give rise to **cis-trans isomerism**, also called **geometric isomerism**. If two similar groups bonded to the carbons of the double bond are on the same side of the bond, the alkene is the **cis** isomer. If the similar groups are on opposite sides of the bond, the alkene is **trans**. Not all alkenes are capable of showing cis-trans isomerism. If either carbon of the double bond holds two identical groups, the molecule cannot have cis and trans forms. Following are some cis and trans alkenes and some alkenes that cannot show cis-trans isomerism.



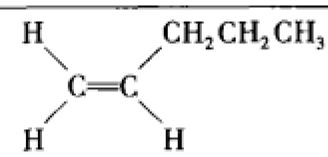
cis-2-pentene
cis-pent-2-ene
(顺-2-戊烯)



trans-2-pentene
trans-pent-2-ene
(反-2-戊烯)



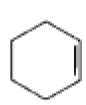
2-methyl-2-pentene
2-methylpent-2-ene



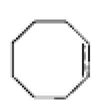
1-pentene
pent-1-ene

(neither cis nor trans)

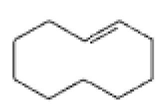
Trans cycloalkenes are unstable unless the ring is large enough (at least eight carbon atoms) to accommodate the trans double bond. Therefore, all cycloalkenes are assumed to be cis unless they are specifically named trans. The cis name is rarely used with cycloalkenes, except to distinguish a large cycloalkene from its trans isomer.



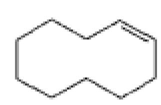
cyclohexene
(环己烯)



cyclooctene
(环辛烯)



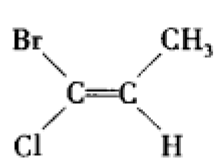
trans-cyclodecene
(反-环癸烯)

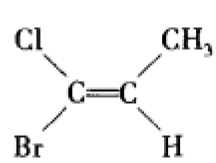


cis-cyclodecene
(顺-环癸烯)

3-5C *E-Z* Nomenclature

The cis-trans nomenclature for geometric isomers sometimes fails to give an unambiguous name. For example, the isomers of 1-bromo-1-chloropropene are not clearly cis or trans because it is not obvious which substituents are referred to as being cis or trans.





geometric isomers of 1-bromo-1-chloropropene (1-氯-1-溴丙烯)

To deal with this problem, we use the ***E-Z* system** of nomenclature for cis-trans isomers. To name an alkene by the *E-Z* system, mentally separate the double bond into its two ends. Consider each end of the double bond sepa-

rately, and use the Cahn-Ingold-Prelog rules to assign first and second priorities to the two substituent groups on that end. Do the same for the other end of the double bond.

The Cahn-Ingold-Prelog rules are as follows:

(a) Look at the first atom of the group—the atom bonded to the asymmetric carbon. *Atoms with higher atomic numbers receive higher priorities*. For example, if the four groups bonded to an asymmetric carbon atom were H, CH_3, NH_2, and F, the fluorine atom (atomic number 9) would have the highest priority, followed by the nitrogen atom of the NH_2 group (atomic number 7), then by the carbon atom of the methyl group (atomic number 6). Note that we look only at the atomic number of the atom directly attached to the asymmetric carbon, not the entire group. Hydrogen would have the lowest priority.

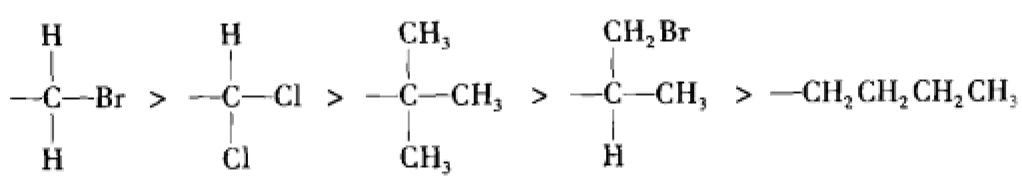
With different isotopes of the same element, the heavier isotopes have higher priorities. For example, tritium (^3H) receives a higher priority than deuterium (^2H), followed by hydrogen (^1H).

Examples of priority for atoms bonded to an asymmetric carbon:

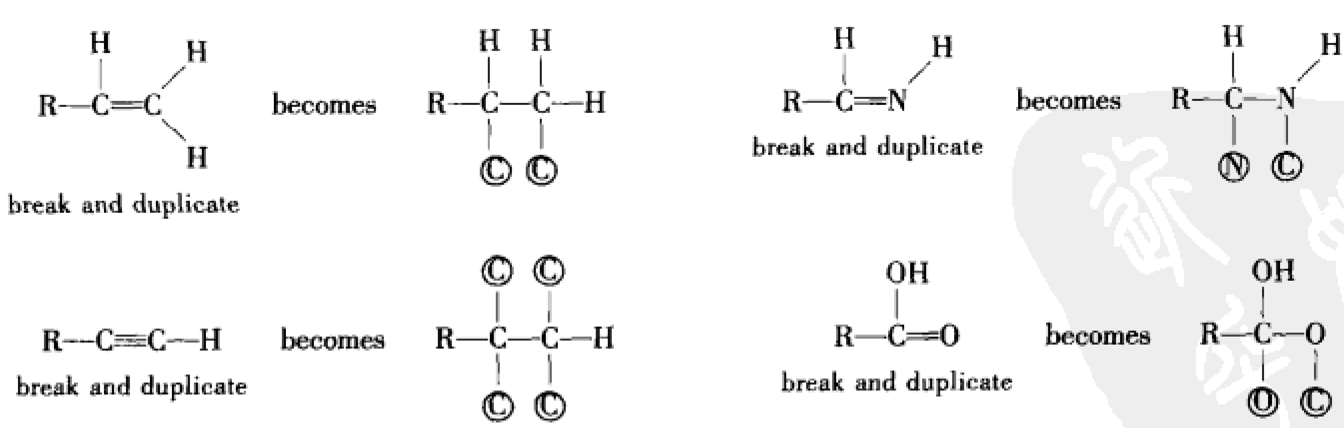
$$I > Br > Cl > S > F > O > N > {}^{13}C > {}^{12}C > Li > {}^{3}H > {}^{2}H > {}^{1}H$$

(b) *In case of ties, use the next atoms along the chain of each group as tiebreakers.* For example, we assign a higher priority to isopropyl $—CH(CH_3)_2$ than to ethyl $—CH_2CH_3$. The first carbon atom in the ethyl group is bonded to two hydrogens and one carbon, while the first carbon in the isopropyl group is bonded to two carbons and one hydrogen. An ethyl group and a $—CH_2CH_2Br$ have identical first atoms and second atoms, but the bromine atom in the third position gives $—CH_2CH_2Br$ a higher priority than $—CH_2CH_3$. One high-priority atom takes priority over any number of lower-priority atoms.

Examples



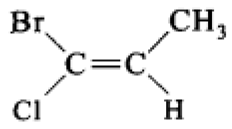
(c) *Treat double and triple bonds as if each were a bond to a separate atom.* For this method, imagine that each pi bond is broken and the atoms at both ends duplicated. Note that when you break a bond, you always add *two* imaginary atoms.



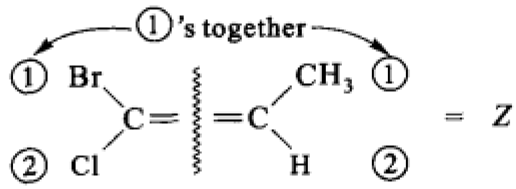
If the two first-priority atoms are *together* (*cis*) on the same side of the double bond, you have the ***Z*** isomer, from the German word *zusammen*, "together." If the two first-priority atoms are on *opposite* (*trans*) sides of the double bond, you have the ***E*** isomer, from the German word *entgegen*, "opposite."

Zusammen (顺) *Entgegen* (反)

For example,

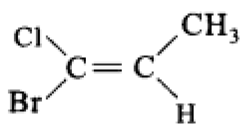


becomes

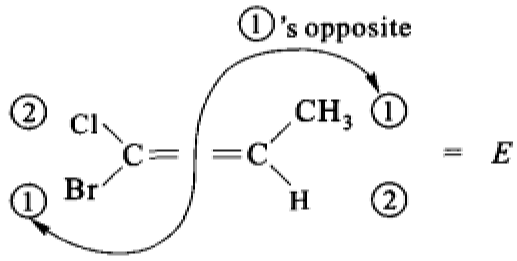


(*Z*)-1-bromo-1-chloropropene
(顺-1-氯-1-溴丙烯)

The other isomer is named similarly:

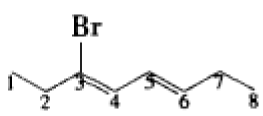


becomes



(*E*)-1-bromo-1-chloropropene
(反-1-氯-1-溴丙烯)

If the alkene has more than one double bond, the stereochemistry about each double bond should be specified. The following compound is properly named 3-bromo-(3*Z*, 5*E*)-octadiene:



3-bromo-(3*Z*, 5*E*)-octadiene [3-溴-(3*Z*, 5*E*)-辛二烯]
3-bromo-(3*Z*, 5*E*)-octa-3,5-diene

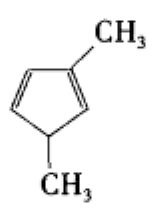
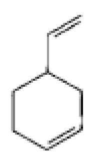
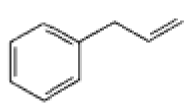
The use of *E*-*Z* names (rather than cis and trans) is always an option, but it is required whenever a double bond is not clearly cis or trans. Most trisubstituted and tetrasubstituted double bonds are more clearly named *E* or *Z* rather than cis or trans.

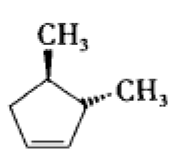
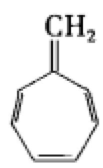
PROBLEM 3-6

Give the systematic (IUPAC) names of the following alkenes.

(a) $CH_2{=}CH{-}CH_2{-}CH(CH_3)_2$ (b) $CH_3(CH_2)_3{-}C(=CH_2){-}CH_2CH_3$

(c) $CH_2{=}CH{-}CH_2{-}CH{=}CH_2$ (d) $CH_2{=}C{=}CH{-}CH{=}CH_2$

(e)  (f)  (g) 

(h)  (i) 

PROBLEM 3-7

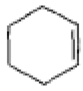
Each of the following names is incorrect. Draw the structure represented by the incorrect name (or a consistent structure if the name is ambiguous), and give your drawing the correct name.

(a) *cis*-2,3-dimethyl-2-pentene
(b) 3-vinylhex-4-ene
(c) 2-methylcyclopentene
(d) 6-chlorocyclohexadiene
(e) 3,4-dimethylcyclohexene
(f) *cis*-2,5-dibromo-3-ethylpent-2-ene

PROBLEM 3-8

Some of the following examples can show geometric isomerism, and some cannot. For the ones that can, draw all the geometric isomers, and assign complete names using the *E-Z* system.

(a) 3-bromo-2-chloro-2-pentene
(b) 3-ethylhexa-2,4-diene
(c) 3-bromo-2-methyl-2-butene
(d) 1,3-pentadiene
(e) 4-*t*-butyl-5-methyl-4-octene
(f) 3,7-dichloroocta-2,5-diene

(g) 
cyclohexene

(h)
cyclodecene

(i)
1,5-cyclodecadiene

3-6 Nomenclature of Alkynes

IUPAC Names The IUPAC nomenclature for alkynes is similar to that for alkenes. We find the longest continuous chain of carbon atoms that includes the triple bond and change the *-ane* ending of the parent alkane to *-yne*. The chain is numbered from the end closest to the triple bond, and the position of the triple bond is designated by its lowernumbered carbon atom. Substituents are given numbers to indicate their locations.

	$H—C{\equiv}C—H$	$CH_3—C{\equiv}C—H$	$CH_3—C{\equiv}C—CH_3$	$CH_3—CH(CH_3)—C{\equiv}C—CH_2—CH(Br)—CH_3$
IUPAC name:	ethyne (乙炔) (acetylene)	propyne (丙炔)	2-butyne (2－丁炔) but-2-yne	6-bromo-2-methyl-3-heptyne 6-bromo-2-methylhept-3-yne (2－甲基－6－溴－3－庚炔)

When additional functional groups are present, the suffixes are combined to produce the compound names of the *alkenynes* (a double bond and a triple bond), *alkynols* (a triple bond and an alcohol), and so on. The new IUPAC system (placing the number right before the group) helps to clarify these names. The IUPAC rules give alkenes and alcohols higher priority than alkynes, so the numbering begins at the end closer to these higher-priority groups.

	$H_2C{=}C(CH_3)—C{\equiv}C—CH_3$	$CH_3—CH(OH)—C{\equiv}C—H$	$CH_3—C{\equiv}C—CH(OCH_3)—CH_2CH_3$
IUPAC name:	2-methyl-1-penten-3-yne	3-butyn-2-ol	4-methoxy-2-hexyne
new IUPAC name:	2-methylpent-1-en-3-yne (2－甲基－1－戊烯－3－炔)	but-3-yn-2-ol (3－丁炔－2－醇)	4-methoxyhex-2-yne (4－甲氧基－2－己炔)

Common Names The common names of alkynes describe them as derivatives of acetylene. Most alkynes can be named as a molecule of acetylene with one or two alkyl substituents. This nomenclature is like the common nomenclature for ethers, where we name the two alkyl groups bonded to oxygen.

$H—C{\equiv}C—H$	$R—C{\equiv}C—H$	$R—C{\equiv}C—R'$
acetylene	an alkylacetylene (烷基乙炔)	a dialkylacetylene (二烷基乙炔)

$CH_3—C≡C—H$ methylacetylene (甲基乙炔)	$Ph—C≡C—H$ phenylacetylene (苯基乙炔)	$CH_3—C≡C—CH_2CH_3$ ethylmethylacetylene (甲基乙基乙炔)
$(CH_3)_2CH—C≡C—CH(CH_3)_2$ diisopropylacetylene (二异丙基乙炔)	$Ph—C≡C—Ph$ diphenylacetylene (二苯基乙炔)	$H—C≡C—CH_2OH$ hydroxymethylacetylene (propargyl alcohol) (羟甲基乙炔,炔丙醇)

Many of an alkyne's chemical properties depend on whether there is an acetylenic hydrogen (H—C≡C), that is, whether the triple bond comes at the end of a carbon chain. Such an alkyne is called a **terminal alkyne** or a **terminal acetylene**. If the triple bond is located somewhere other than the end of the carbon chain, the alkyne is called an **internal alkyne** or an **internal acetylene**.

acetylenic hydrogen	(no acetylenic hydrogen)
$\boxed{H}—C≡C—CH_2CH_3$ 1-butyne, a *terminal* alkyne (1-丁炔,端炔烃)	$CH_3—C≡C—CH_3$ 2-butyne, an *internal* alkyne (2-丁炔,内炔烃)

PROBLEM 3-9

For each molecular formula, draw all the isomeric alkynes, and give their IUPAC names. Circle the acetylenic hydrogen of each terminal alkyne.

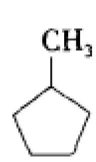
(a) C_4H_6 (two isomers) (b) C_5H_8 (three isomers)

3-7 Nomenclature of Cycloalkanes

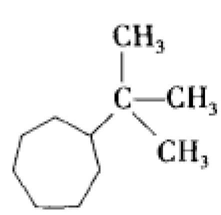
3-7A IUPAC Names

Cycloalkanes are alkanes that contain rings of carbon atoms. Simple cycloalkanes are named like acyclic (noncyclic) alkanes, with the prefix *cyclo-* indicating the presence of a ring. For example, the cycloalkane with four carbon atoms in a ring is called *cyclobutane*. The cycloalkane with seven carbon atoms in a ring is *cycloheptane*. Line-angle formulas are often used for drawing the rings of cycloalkanes (Figure 3-1).

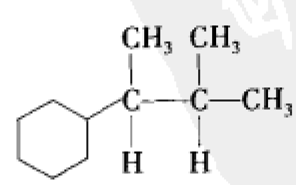
Substituted cycloalkanes use the cycloalkane for the base name, with the alkyl groups named as substituents. If there is just one substituent, no numbering is needed.



methylcyclopentane
(甲基环戊烷)

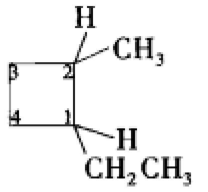


t-butylcycloheptane
(叔丁基环庚烷)

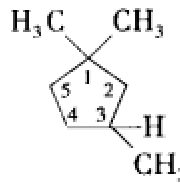


(1,2-dimethylpropyl) cyclohexane
(1,2-二甲基丙基)环己烷

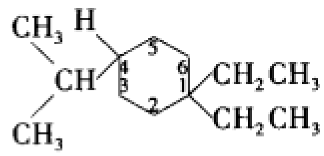
If there are two or more substituents on the ring, the ring carbons are numbered to give the lowest possible numbers for the substituted carbons. The numbering begins with one of the substituted ring carbons and continues in the direction that gives the lowest possible numbers to the other substituents. In the name, the substituents are listed in alphabetical order. When the numbering could begin with either of two alkyl groups (as in a disubstituted cycloalkane), begin with the one that is alphabetically first.



1-ethyl-2-methylcyclobutane
(2－甲基－1－乙基环丁烷)

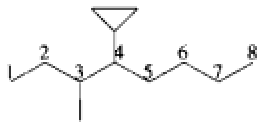


1,1,3-trimethylcyclopentane
(1,1,3－三甲基环戊烷)

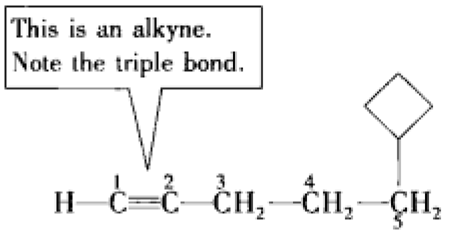


1,1-diethyl-4-isopropylcyclohexane
(1,1－二乙基－4－异丙基环己烷)

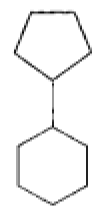
When the acyclic portion of the molecule contains more carbon atoms than the cyclic portion (or when it contains an important functional group), the cyclic portion is sometimes named as a cycloalkyl substituent.



4-cyclopropyl-3-methyloctane
(3－甲基－4－环丙基辛烷)



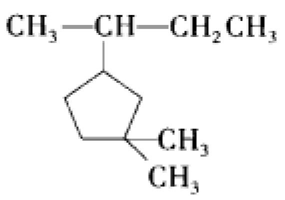
5-cyclobutyl-1-pentyne
(5－环丁基－1－戊炔)

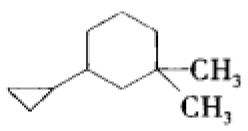


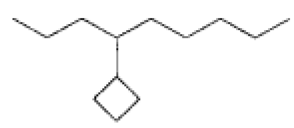
cyclopentylcyclohexane
(环戊基环己烷)

PROBLEM 3-10

Give IUPAC names for the following compounds.

(a) 

(b) 

(c) 

PROBLEM 3-11

Draw the structure and give the molecular formula for each of the following compounds.

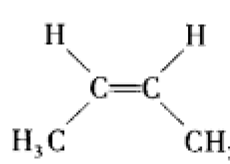
(a) cyclododecane (b) propylcyclohexane

(c) cyclopropylcyclopentane (d) 3-ethyl-1,1-dimethylcyclohexane

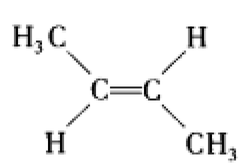
3-7B Cis-trans Isomerism in Cycloalkanes

Open-chain alkanes undergo rotations about their carbon-carbon single bonds, so they are free to assume any of an infinite number of conformations. Alkenes have rigid double bonds that prevent rotation, giving rise to cis and trans isomers with different orientations of the groups on the double bond (Section 2-8). Cycloalkanes are similar to alkenes in this respect. A cycloalkane has two distinct faces. If two substituents point toward the same face, they are **cis**. If they point toward opposite faces, they are **trans**. These **geometric isomers** cannot interconvert without breaking and re-forming bonds.

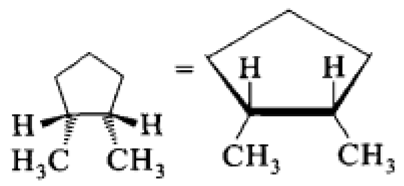
Figure 3-4 compares the cis-trans isomers of 2-butene with those of 1,2-dimethylcyclopentane. Make models of these compounds to convince yourself that *cis*- and *trans*-1,2-dimethylcyclopentane cannot interconvert by simple rotations about the bonds.



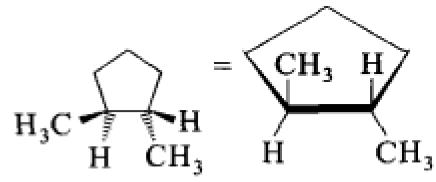
cis-2-butene
(顺－2－丁烯)



trans-2-butene
(反－2－丁烯)



cis-1,2-dimethylcyclopentane
(顺-1,2-二甲基环戊烷)

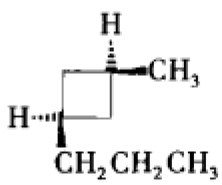


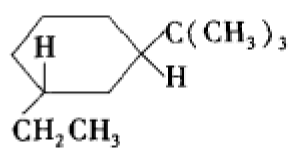
trans-1,2-dimethylcyclopentane
(反-1,2-二甲基环戊烷)

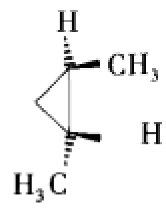
Figure 3-4 Cis-trans isomerism in cycloalkanes. Like alkenes, cycloalkane rings are restricted from free rotation. Two substituents on a cycloalkane must be either on the same side (cis) or on opposite sides (trans) of the ring.

PROBLEM 3-12

Give IUPAC names for the following cycloalkanes.

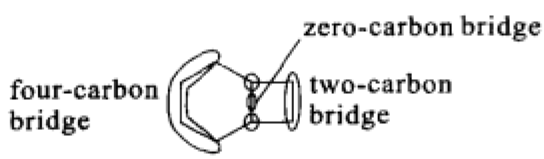
(a) 

(b) 

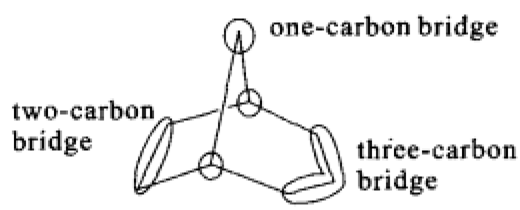
(c) 

3-7C Nomenclature of Bicyclic Alkanes

The name of a **bicyclic alkanes** is based on the name of the alkane having the same number of carbons as there are in the ring system. This name follows the prefix *bicyclo* and a set of brackets enclosing three numbers. The following examples contain eight carbon atoms and are named bicyclo[4.2.0]octane and bicyclo[3.2.1]octane, respectively.



bicyclo[4.2.0]octane
(二环[4.2.0]辛烷)

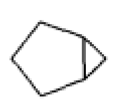


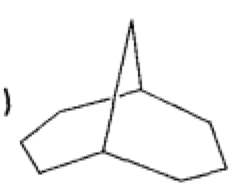
bicyclo[3.2.1]octane
(二环[3.2.1]辛烷)

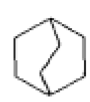
All fused and bridged bicyclic systems have three bridges connecting the two bridgehead atoms where the rings connect. The numbers in the brackets give the number of carbon atoms in each of the three bridges connecting the bridgehead carbons, in order of decreasing size.

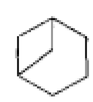
PROBLEM 3-13

Name the following compounds.

(a) 

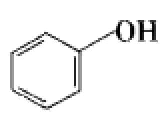
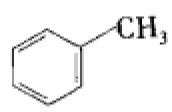
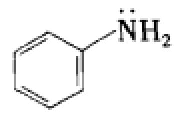
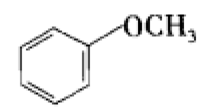
(b) 

(c) 

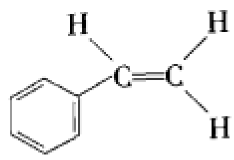
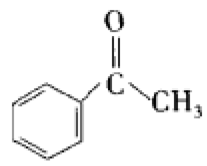
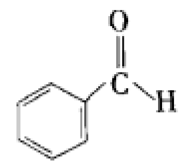
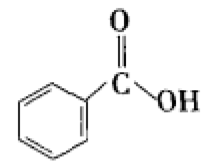
(d) 

3-8 Nomenclature of Benzene Derivatives

Benzene derivatives have been isolated and used as industrial reagents for well over 100 years. Many of their names are rooted in the historical traditions of chemistry. The following compounds are usually called by their historical common names, and almost never by the systematic IUPAC names:

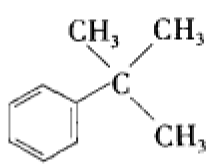
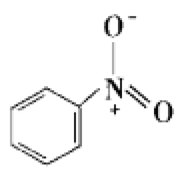
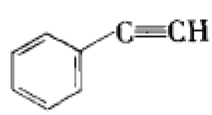
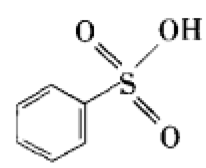





common name: phenol（苯酚）(benzenol) toluene（甲苯）(methylbenzene) aniline（苯胺）(benzenamine) anisole（茴香醚,甲基苯基醚）(methoxybenzene)

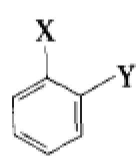
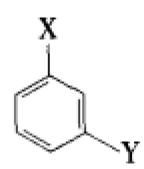
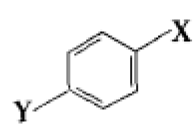
common name: styrene（苯乙烯）(vinylbenzene) acetophenone（苯乙酮）(methyl phenyl ketone) benzaldehyde（苯甲醛） benzoic acid（苯甲酸）

Many compounds are named as derivatives of benzene, with their substituents named just as though they were attached to an alkane.

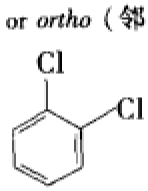
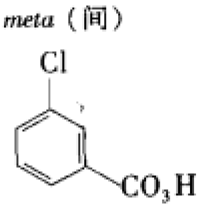
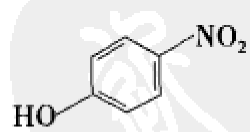





tert-butylbenzene（叔丁基苯） nitrobenzene（硝基苯） ethynylbenzene (phenylacetylene)（乙炔基苯,苯乙炔） benzenesulfonic acid（苯磺酸）

Disubstituted benzenes are named using the prefixes ***ortho-***, ***meta-***, and ***para-*** to specify the substitution patterns. These terms are abbreviated *o-*, *m-*, and *p-*. Numbers can also be used to specify the substitution in disubstituted benzenes.

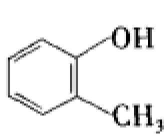
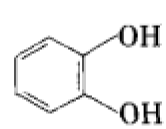
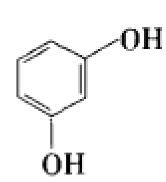
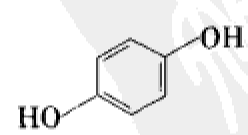




1,2 or *ortho*（邻） 1,3 or *meta*（间） 1,4 or *para*（对）

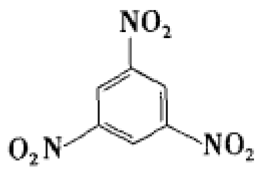
common name:	*o*-dichlorobenzene	*m*-chloroperoxybenzoic acid	*p*-nitrophenol
IUPAC name:	1,2-dichlorobenzene	3-chloroperoxybenzoic acid	4-nitrophenol
	（邻二氯苯）	（间氯过氧苯甲酸）	（对硝基苯酚）

The methylphenols are called *cresols*, while the names of the benzenediols are based on their historical uses and sources rather than their structures. We will generally use the systematic names of phenolic compounds.

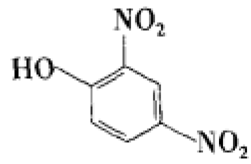





IUPAC name:	2-methylphenol	benzene-1,2-diol	benzene-1,3-diol	benzene-1,4-diol
common name:	*ortho*-cresol	catechol	resorcinol	hydroquinone
	（邻甲苯酚）	（邻苯二酚,儿茶酚）	（间苯二酚,雷锁酚）	（对苯二酚,氢醌）

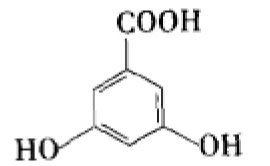
With three or more substituents on the benzene ring, numbers are used to indicate their positions. Assign the numbers as you would with a substituted cyclohexane, to give the lowest possible numbers to the substituents. The carbon atom bearing the functional group that defines the base name (as in phenol or benzoic acid) is assumed to be C1.



1,3,5-trinitrobenzene
(1,3,5-三硝基苯)

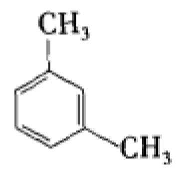


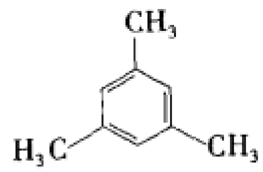
2,4-dinitrophenol
(2,4-二硝基苯酚)

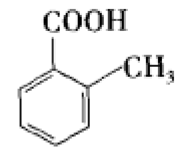


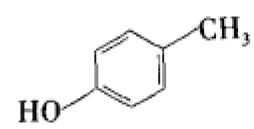
3,5-dihydroxybenzoic acid
(3,5-二羟基苯甲酸)

Many disubstituted benzenes (and polysubstituted benzenes) have historical names. Some of these are obscure, with no obvious connection to the structure of the molecule.



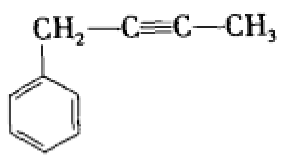




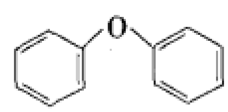


common name:	*m*-xylene	mesitylene	*o*-toluic acid	*p*-cresol
IUPAC name:	1,3-dimethylbenzene	1,3,5-trimethylbenzene	2-methylbenzoic acid	4-methylphenol
	(间二甲苯)	(均三甲苯)	(邻甲基苯甲酸)	(对甲苯酚)

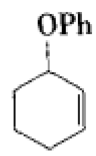
When the benzene ring is named as a substituent on another molecule, it is called a **phenyl group**. The phenyl group is used in the name just like the name of an alkyl group, and it is often abbreviated **Ph** (or ϕ) in drawing a complex structure.



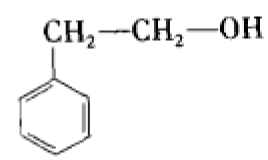
or Ph—CH_2—C≡C—CH_3
1-phenyl-2-butyne
(1-苯基-2-丁炔)



or Ph_2O
diphenyl ether
二苯基醚

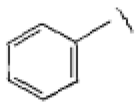


3-phenoxycyclohexene
(3-苯氧基环己烯)

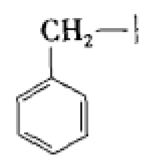


or $PhCH_2CH_2OH$
2-phenylethanol
(2-苯基乙醇)

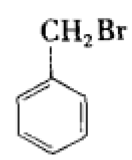
The seven-carbon unit consisting of a benzene ring and a methylene (—CH_2—) group is often named as a **benzyl group**. Be careful not to confuse the *benzyl group* (seven carbons) with the *phenyl group* (six carbons).



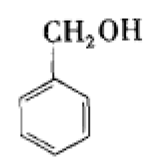
a phenyl group
(苯基)



a benzyl group
(苄基)



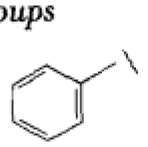
benzyl bromide
(α-bromotoluene)
(苄溴,α-溴代甲苯)



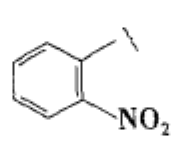
benzyl alcohol
(苄醇)

Aromatic hydrocarbons are sometimes called **arenes**. An **aryl group**, abbreviated **Ar**, is the aromatic group that remains after the removal of a hydrogen atom from an aromatic ring. The phenyl group, **Ph**, is the simplest aryl group. The generic aryl group (**Ar**) is the aromatic relative of the generic alkyl group, which we symbolize by **R**.

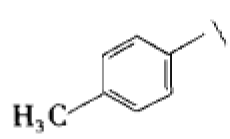
Examples of aryl groups



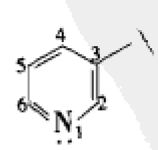
the phenyl group



the *o*-nitrophenyl group
(邻硝基苯基)



the *p*-tolyl group
(对甲苯基)



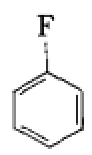
the 3-pyridyl group
(3-吡啶基)

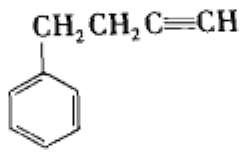
Examples of the use of a generic aryl group

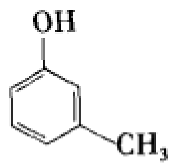
Ar—MgBr	Ar_2O or Ar—O—Ar′	Ar—NH_2	Ar—SO_3H
an arylmagnesium bromide	a diaryl ether	an arylamine	an arylsulfonic acid
(溴化芳基镁)	(二芳基醚)	(芳基胺)	(芳基磺酸)

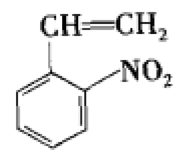
PROBLEM 3-14

Name the following compounds:

(a) 

(b) 

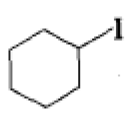
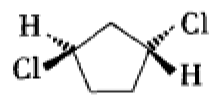
(c) 

(d) 

3-9 Nomenclature of Alkyl Halides

There are two ways of naming alkyl halides. The systematic (IUPAC) nomenclature treats an alkyl halide as an alkane with a *halo*-substiuent: Fluorine is *fluoro*-, chlorine is *chloro*-, bromine is *bromo*-, and iodine is *iodo*-. The result is a systematic **haloalkane** name, as in 1-chlorobutane or 2-bromopropane. Common or "trivial" names are constructed by naming the alkyl group and then the halide, as in "isopropyl bromide." This is the origin of the term *alkyl halide*. Common names are useful only for simple alkyl halides, such as the following:

	CH_3CH_2—F	$CH_2(Cl)CH_2CH_2CH_3$	CH_3—CH(Br)—CH_3
IUPAC name:	fluoroethane (氟乙烷)	1-chlorobutane (1-氯丁烷)	2-bromopropane (2-溴丙烷)
common name:	ethyl fluoride (乙基氟)	*n*-butyl chloride (正丁基氯)	isopropyl bromide (异丙基溴)

		
IUPAC name:	iodocyclohexane (碘代环己烷)	*trans*-1,3-dichlorocyclopentane (反-1,3-二氯环戊烷)
common name:	cyclohexyl iodide (环己基碘)	(none)

	CH_3CH_2—CH(CH_2—I)—CH_2CH_3	$CH_3CH_2CH_2$—CH(CH_2CH_2—F)—$CH_2CH_2CH_3$
IUPAC name:	3-(iodomethyl)pentane [3-(碘甲基)戊烷]	4-(2-fluoroethyl)heptane [4-(2-氟乙基)庚烷]

Some of the halomethanes have acquired common names that are not clearly related to their structures. A compound of formula CH_2X_2 (a methylene group with two halogens) is called a *methylene halide*; a compound of formula CHX_3 is called a *haloform*; and a compound of formula CX_4 is called a *carbon tetrahalide*.

	CH_2Cl_2	$CHCl_3$	CCl_4
IUPAC name:	dichloromethane	trichloromethane	tetrachloromethane
common name:	methylene chloride (二氯甲烷)	chloroform (氯仿)	carbon tetrachloride (四氯化碳)

Alkyl halides are classified according to the nature of the carbon atom bonded to the halogen. If the halogen-bearing carbon is bonded to one carbon atom, it is primary (1°) and the alkyl halide is a **primary halide**. If

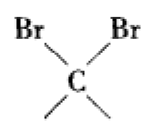
two carbon atoms are bonded to the halogen-bearing carbon, it is secondary (2°) and the compound is a **secondary halide**. A **tertiary halide** (3°) has three other carbon atoms bonded to the halogen-bearing carbon atom. If the halogen-bearing carbon atom is a methyl group (bonded to no other carbon atoms), the compound is a *methyl halide*.

methyl halide	primary (1°) halide	secondary (2°) halide	tertiary (3°) halide
(甲基卤代烷)	(伯卤代烷)	(仲卤代烷)	(叔卤代烷)

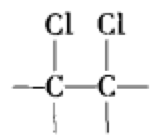
Examples

	CH_3—Br	$CH_3CH_2CH_2$—F	2-iodobutane structure	$(CH_3)_3C$—Cl
		1°	2°	3°
IUPAC name:	bromomethane	1-fluoropropane	2-iodobutane	2-chloro-2-methylpropane
	(溴甲烷)	(1-氟丙烷)	(2-碘丁烷)	(2-甲基-2-氯丙烷)
common name:	methyl bromide (甲基溴)	*n*-propyl fluoride (正丙基氟)	*sec*-butyl iodide (仲丁基碘)	*t*-butyl chloride (叔丁基氯)

A **geminal dihalide** (Latin, *geminus* "twin") has the two halogen atoms bonded to the same carbon atom. A **vicinal dihalide** (Latin, *vicinus* "neighboring") has the two halogens bonded to adjacent carbon atoms.



a geminal dibromide
(偕二溴)



a vicinal dichloride
(邻二氯)

PROBLEM 3-15

For each of the following compounds,

1. Give the IUPAC name.
2. Give the common name (if possible).
3. Classify the compound as a methyl, primary, secondary, or tertiary halide.

(a) $(CH_3)_2CH—CH_2Cl$

(b) CH_2I_2

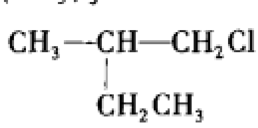
(c) $CH_3—CHCl_2$

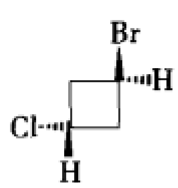
(d) $BrCH_2—CCl_3$

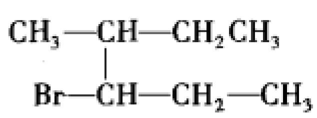
(e) $CHCl_3$

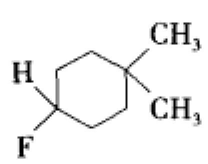
(f) $(CH_3)_3C—Br$

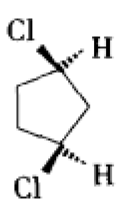
(g) $CH_3—CH_2—CHBr—CH_3$

(h) 

(i) 

(j) 

(k) 

(l) 

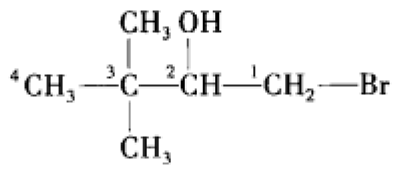
3–10 Nomenclature of Alcohols and Thiols

3–10A IUPAC Names ("Alkanol" Names)

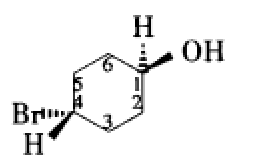
The IUPAC system provides unique names for alcohols, based on rules that are similar to those for other classes of compounds. In general, the name carries the *-ol* suffix, together with a number to give the location of the hydroxyl group. The formal rules are summarized in the following three steps:

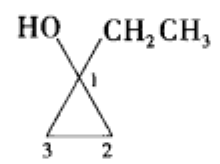
1. Name the longest carbon chain that contains the carbon atom bearing the —OH group. Drop the final *-e* from the alkane name and add the suffix *-ol* to give the root name.
2. Number the longest carbon chain starting at the end nearest the hydroxyl group, and use the appropriate number to indicate the position of the —OH group. (The hydroxyl group takes precedence over double and triple bonds.)
3. Name all the substituents and give their numbers, as you would for an alkane or an alkene.

In the following example, the longest carbon chain has four carbons, so the root name is *butanol*. The —OH group is on the second carbon atom, so this is a 2-butanol. The complete IUPAC name is 1-bromo-3,3-dimethyl-2-butanol. The new IUPAC positioning of numbers would place the 2 next to the group it locates (*-ol*), giving the name 1-bromo-3,3-dimethylbutan-2-ol.



Cyclic alcohols are named using the prefix *cyclo-*; the hydroxyl group is assumed to be on C1.

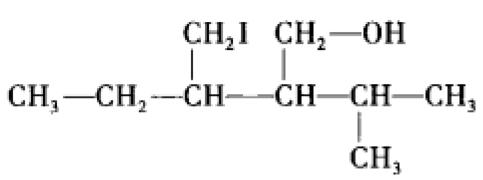




IUPAC name:	*trans*-4-bromocyclohexanol	1-ethylcyclopropanol
new IUPAC name:	*trans*-4-bromocyclohexan-1-ol	1-ethylcyclopropan-1-ol
	(反-4-溴环己醇)	(1-乙基环丙醇)

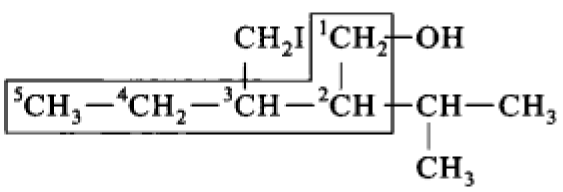
SOLVED PROBLEM 3–2

Give the systematic (IUPAC) name for the following alcohol.



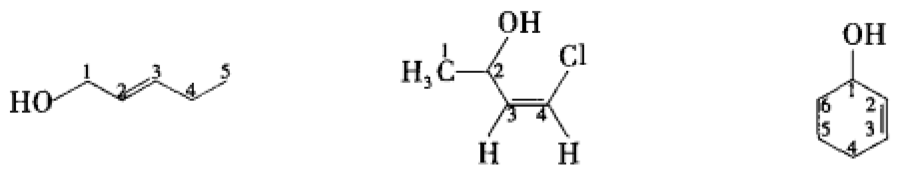
SOLUTION

The longest chain contains six carbon atoms, but it does not contain the carbon bonded to the hydroxyl group. The longest chain containing the carbon bonded to the —OH group is the one outlined by the green box, containing five carbon atoms. This chain is numbered from right to left in order to give the hydroxyl-bearing carbon atom the lowest possible number.



The correct name for this compound is 3-(iodomethyl)-2-isopropylpentan-1-ol.

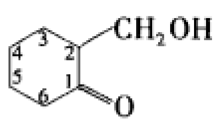
In naming alcohols containing double and triple bonds, use the *-ol* suffix after the alkene or alkyne name. The alcohol functional group takes precedence over double and triple bonds, so the chain is numbered in order to give the lowest possible number to the carbon atom bonded to the hydroxyl group. The position of the —OH group is given by putting its number before the *-ol* suffix. Numbers for the multiple bonds were once given early in the name, but the 1997 revision of the IUPAC rules puts them next to the *-en* or *-yn* suffix they describe. Both the new and old placements of the numbers are shown in the following figure.



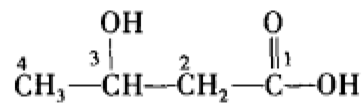
IUPAC name:	*trans*-2-penten-1-ol	(*Z*)-4-chloro-3-buten-2-ol	2-cyclohexen-1-ol
new IUPAC name:	*trans*-pent-2-en-1-ol	(*Z*)-4-chlorobut-3-en-2-ol	cyclohex-2-en-1-ol
	(反-2-戊烯-1-醇)	(*Z*)-4-氯-3-丁烯-2-醇	(2-环己烯-1-醇)

Table 3-3 is a partial table showing the order of precedence of functional groups for assigning IUPAC names. In general, the highest-priority functional group is considered the "main" group, and the others are treated as substituents.

The —OH functional group is named as a **hydroxy** substituent when it appears on a structure with a higher-priority functional group or when the structure is too difficult to name as a simple alcohol.



2-hydroxymethylcyclohexanone
(2-羟甲基环己酮)



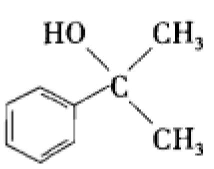
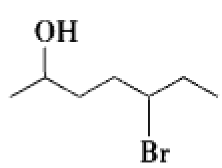
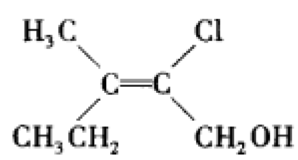
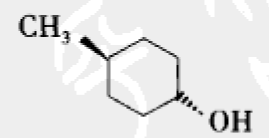
3-hydroxybutanoic acid
(3-羟基丁酸)

TABLE 3-3 Priority of Functional Groups in Naming Organic Compounds (decreasing priority)

acids	酸	amines	胺
esters	酯	alkenes	烯烃
amides	酰胺	alkynes	炔烃
nitriles	腈	alkanes	烷烃
aldehydes	醛	ethers	醚
ketones	酮	halides	卤代烃
alcohols	醇		

PROBLEM 3-16

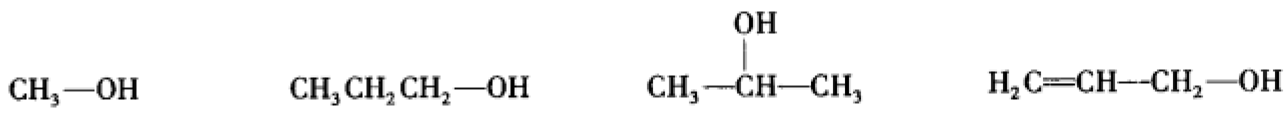
Give the IUPAC names of the following alcohols.

(a)  (b)  (c)  (d) 

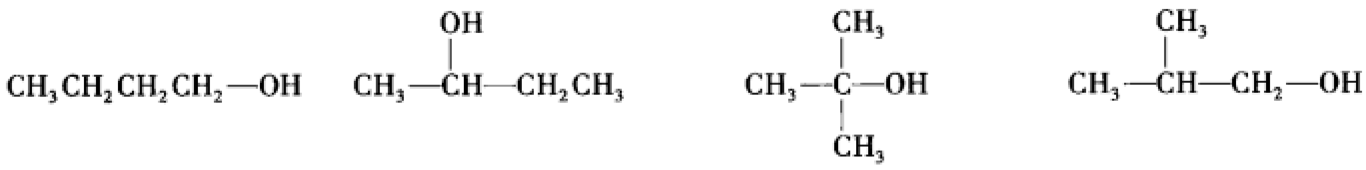
3-10B Common Names of Alcohols

The common name of an alcohol is derived from the common name of the alky group and the word *alcohol*. This system pictures an alcohol as a molecule of water with an alkyl group replacing one of the hydrogen atoms. If the

structure is complex, the common nomenclature becomes awkward, and the IUPAC nomenclature should be used.



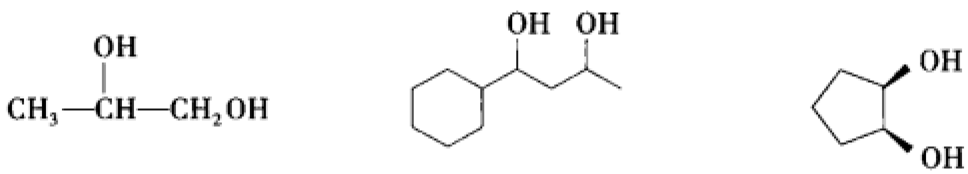
common name:	methyl alcohol	*n*-propyl alcohol（正丙醇）	isopropyl alcohol（异丙醇）	allyl alcohol（烯丙基醇）
IUPAC name:	methanol（甲醇）	1-propanol（1－丙醇）	2-propanol（2－丙醇）	2-propen-1-ol（2－丙烯－1－醇）



common name:	*n*-butyl alcohol（正丁醇）	*sec*-butyl alcohol（仲丁醇）	*t*-butyl alcohol（叔丁醇）	isobutyl alcohol（异丁醇）
IUPAC name:	1-butanol（1－丁醇）	2-butanol（2－丁醇）	2-methyl-2-propanol	2-methyl-1-propanol

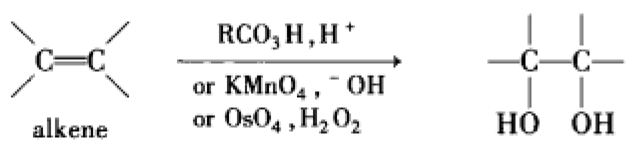
3－10C Names of Diols

Alcohols with two —OH groups are called **diols** or **glycols**. They are named like other alcohols except that the suffix *diol* is used and two numbers are needed to tell where the two hydroxyl groups are located. This is the preferred, systematic (IUPAC) method for naming diols.



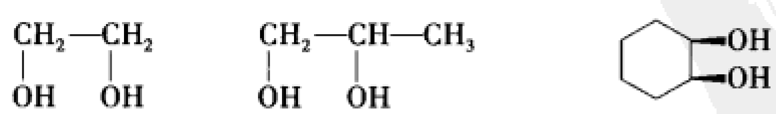
IUPAC name:	propane-1,2-diol（1,2－丙二醇）	1-cyclohexylbutane-1,3-diol（1－环己基－1,3－丁二醇）	*cis*-cyclopentane-1,2-diol（顺－1,2－环戊二醇）

The term *glycol* generally means a 1,2-diol, or **vicinal diol**, with its two hydroxyl groups on adjacent carbon atoms. Glycols are usually synthesized by the hydroxylation of alkenes, using peroxyacids, osmium tetroxide, or potassium permanganate (Chapter 9).



alkene（烯烃） vicinal diol (glycol)（邻二醇）

This synthesis of glycols is reflected in their common names. The glycol is named for the alkene from which it is synthesized:



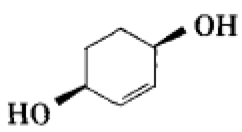
IUPAC name:	ethane-1,2-diol	propane-1,2-diol	*cis*-cyclohexane-1,2-diol
common name:	ethylene glycol	propylene glycol	*cis*-cyclohexene glycol
	（1,2－乙二醇）	（1,2－丙二醇）	（顺－1,2－环己二醇）

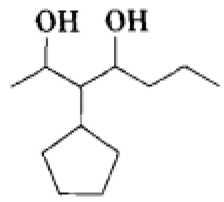
The common names of glycols can be awkward and confusing because the *-ene* portion of the name implies the presence of an alkene double bond, but the glycol does not contain a double bond. We will generally use the IUPAC "diol" nomenclature for diols, but be aware that the names "ethylene glycol" (automotive antifreeze) and "propylene glycol" (used in medicines and foods) are universally accepted for these common diols.

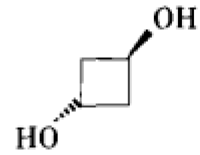
PROBLEM 3-17

Give a systematic (IUPAC) name for each diol.

(a) $CH_3CH(OH)(CH_2)_4CH(OH)C(CH_3)_3$ (b) $HO—(CH_2)_8—OH$

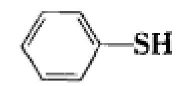
(c) 

(d) 

(e) 

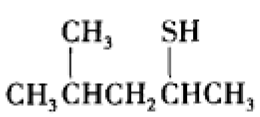
3-10D Names of Thiols

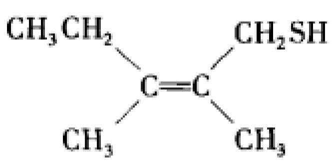
Thiols are sulfur analogues of alcohols, with an —SH group in place of the alcohol —OH group. Oxygen and sulfur are in the same column of the periodic table (group VIA), with oxygen in the second row and sulfur in the third. IUPAC names for thiols are derived from the alkane names, using the suffix *-thiol*. Thiols are also called **mercaptans** ("captures mercury") because they form stable heavy-metal derivatives. Common names are formed like those of alcohols, using the name of the alkyl group with the word *mercaptan*. The —SH group itself is called a *mercapto* group.

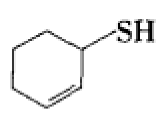
	$CH_3CH_2CH_2CH_2—SH$	$CH_3CH{=}CHCH_2—SH$	$HS—CH_2CH_2—OH$	
IUPAC name:	1-butanethiol	2-butene-1-thiol	2-mercaptoethanol	thiopenol
common name:	*n*-butyl mercaptan			phenylmercaptan (苯硫酚)

PROBLEM 3-18

Give IUPAC names for the following compounds.

(a) 

(b) 

(c) 

3-11 Nomenclature of Ethers and Sulfides

We have been using the common nomenclature of ethers, which is sometimes called the *alkyl alkyl ether* system. The IUPAC system, generally used with more complicated ethers, is sometimes called the *alkoxy alkane* system. Common names are almost always used for simple ethers.

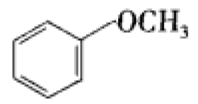
3-11A Common Names (Alkyl Alkyl Ether Names)

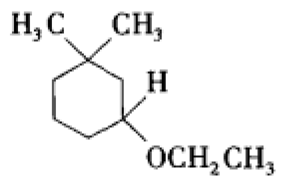
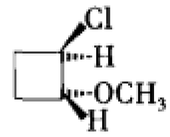
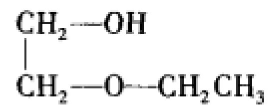
Common names of ethers are formed by naming the two alkyl groups on oxygen and adding the word *ether*. Under the current system, the alkyl groups should be named in alphabetical order, but many people still use the old system, which named the groups in order of increasing complexity. For example, if one of the alkyl groups is methyl and the other is *t*-butyl, the current common name should be "*t*-butyl methyl ether," but most chemists use the older common name, "methyl *t*-butyl ether" (or MTBE). If both groups are methyl, the name is "dimethyl ether." If just one alkyl group is described in the name, it implies the ether is symmetrical, as in "ethyl

ether."

3–11B IUPAC Names (Alkoxy Alkane Names)

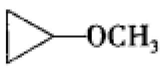
IUPAC names use the more complex alkyl group as the root name, and the rest of the ether as an **alkoxy group**. For example, cyclohexyl methyl ether is named methoxycyclohexane. This systematic nomenclature is often the only clear way to name complex ethers.

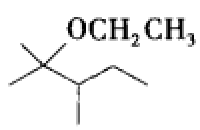
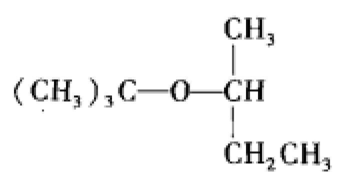
	$CH_3—O—CH_2CH_3$		$Cl—CH_2—O—CH_3$
IUPAC name:	methoxyethane (甲氧基乙烷)	methoxybenzene (甲氧基苯)	chloromethoxymethane (氯甲氧基甲烷)
common name:	ethyl methyl ether (甲基乙基醚)	methyl phenyl ether, anisole (甲基苯基醚,茴香醚)	chloromethyl methyl ether (甲基氯甲基醚)

			
IUPAC name:	3-ethoxy-1,1-dimethylcyclohexane (1,1-二甲基-3-乙氧基环己烷)	*trans*-1-chloro-2-methoxycyclobutane (反-1-氯-2-甲氧基环丁烷)	2-ethoxyethanol (2-乙氧基乙醇)

PROBLEM 3–19

Give a common name and a systematic name for each compound.

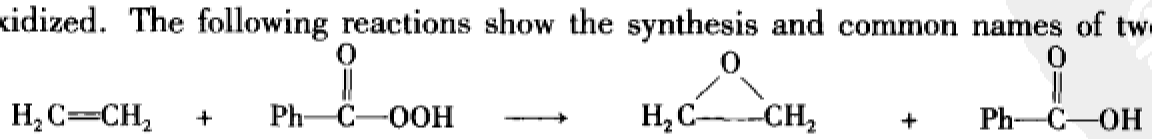
(a)  (b) $CH_3CH_2—O—CH(CH_3)_2$ (c) $ClCH_2CH_2OCH_3$

(d)  (e) 

3–11C Nomenclature of Cyclic Ethers

Cyclic ethers are our first examples of **heterocyclic compounds**, containing a ring in which a ring atom is an element other than carbon. This atom, called the **heteroatom**, is numbered 1 in numbering the ring atoms. Heterocyclic ethers are an especially important and useful class of ethers.

Epoxides (Oxiranes) **Epoxides** are three-membered cyclic ethers, usually formed by peroxyacid oxidation of the corresponding alkenes. The common name of an epoxide is formed by adding "oxide" to the name of the alkene that is oxidized. The following reactions show the synthesis and common names of two simple epoxides.

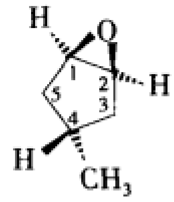


ethylene peroxybenzoic acid (过氧苯甲酸) ethylene oxide (环氧乙烷) benzoic acid (苯甲酸)

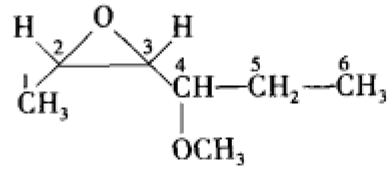
cyclohexene cyclohexene oxide (环氧环己烷)

One systematic method for naming epoxides is to name the rest of the molecule and use the term "epoxy" as

a substituent, giving the numbers of the two carbon atoms bonded to the epoxide oxygen.

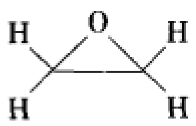


trans-1,2-epoxy-4-methylcyclopantane
(反-4-甲基-1,2-环氧环戊烷)

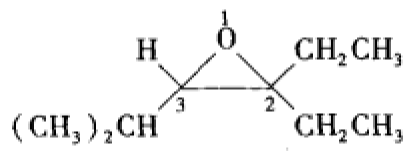


cis-2,3-epoxy-4-methoxyhexane
(顺-4-甲氧基-2,3-环氧己烷)

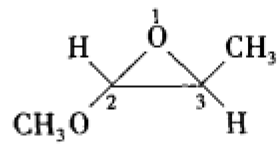
Another systematic method names epoxides as derivatives of the parent compound, ethylene oxide, using "oxirane" as the systematic name for ethylene oxide. In this system, the ring atoms of a heterocyclic compound are numbered starting with the heteroatom and going in the direction to give the lowest substituent numbers.



oxirane
(环氧乙烷)

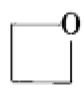


2,2-diethyl-3-isopropyloxirane
(2,2-二乙基-3-异丙基环氧乙烷)

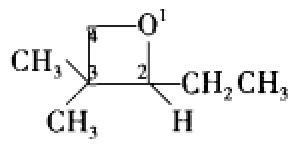


trans-2-methoxy-3-methyloxirane
(反-3-甲基-2-甲氧基环氧乙烷)

Oxetanes The least common cyclic ethers are the four-membered **oxetanes**. Because these four-membered rings are strained, they are more reactive than larger cyclic ethers and open-chain ethers. They are not as reactive as the highly strained oxiranes (epoxides), however.

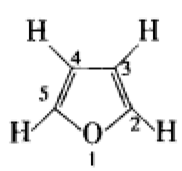


oxetane
(氧杂环丁烷)

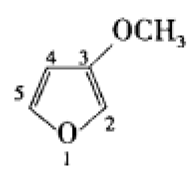


2-ethyl-3,3-dimethyloxetane
(2-乙基-3,3-二甲基氧杂环丁烷)

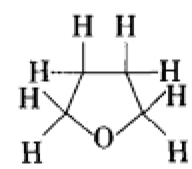
Furans (Oxolanes) The five-membered cyclic ethers are commonly named after an aromatic member of this group, **furan**. We consider the aromaticity of furan and other heterocycles in Chapter 17. The systematic term **oxolane** is also used for a five-membered ring containing an oxygen atom.



furan
(呋喃)



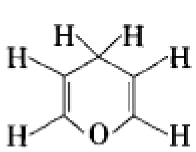
3-methoxyfuran
(3-甲氧基呋喃)



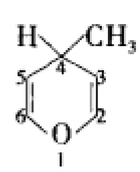
tetrahydrofuran (THF) (四氢呋喃)
(oxolane)

The saturated five-membered cyclic ether resembles furan but has four additional hydrogen atoms. Therefore, it is called *tetrahydrofuran* (THF). One of the most polar ethers, tetrahydrofuran is an excellent nonhydroxylic organic solvent for polar reagents. Grignard reactions sometimes succeed in THF even when they fail in diethyl ether.

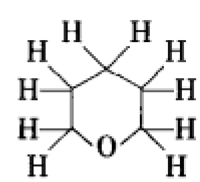
Pyrans (Oxanes) The six-membered cyclic ethers are commonly named as derivatives of **pyran**, an unsaturated ether. The saturated compound has four more hydrogen atoms, so it is called *tetrahydropyran* (THP). The systematic term **oxane** is also used for a six-membered ring containing an oxygen atom.



pyran
(吡喃)

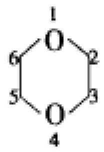


4-methylpyran
(4-甲基吡喃)

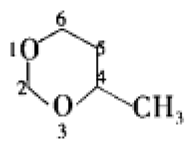


tetrahydropyran (THP) (四氢吡喃)
(oxane)

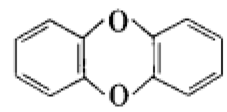
Dioxanes Heterocyclic ethers with two oxygen atoms in a six-membered ring are called **dioxanes**. The most common form of dioxane is the one with the two oxygen atoms in a 1,4-relationship. 1,4-Dioxane is miscible with water, and it is widely used as a polar solvent for organic reactions.



1,4-dioxane
(1,4-二噁烷)

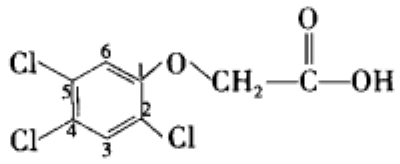


4-methyl-1,3-dioxane
(4-甲基-1,3-二噁烷)

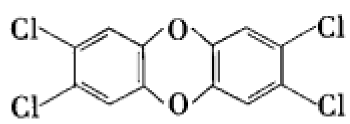


dibenzo-1,4-dioxane (dioxin)
(二苯并-1,4-二噁烷,二氧芑)

Dioxin is a common name for dibenzodioxin, 1,4-dioxane fused with two benzene rings. The name "dioxin" is often used incorrectly in the news media for 2,3,7,8-tetrachlorodibenzodioxin (TCDD), a toxic contaminant in the synthesis of the herbicide called 2,4,5-T or Agent Orange. Surprisingly, TCDD has been in the environment for many millions of years because it is also formed in forest fires. Most dioxins are toxic and carcinogenic (cause cancer) because they associate with DNA and cause a misreading of the genetic code.



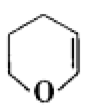
2,4,5-trichlorophenoxyacetic acid
(2,4,5-T or Agent Orange)
(2,4,5-三氯苯氧基乙酸)

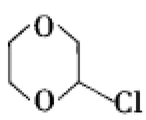


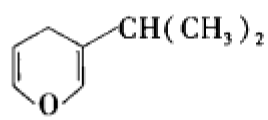
2,3,7,8-tetrachlorodibenzodioxin
(TCDD, incorrectly "dioxin")
(2,3,7,8-四氯二苯并二噁烷)

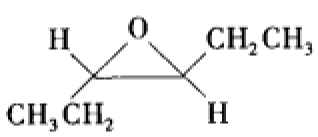
PROBLEM 3-20

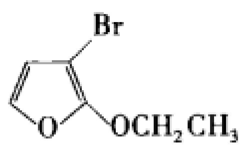
Name the following heterocyclic ethers.

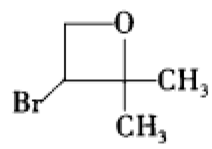
(a) 

(b) 

(c) 

(d) 

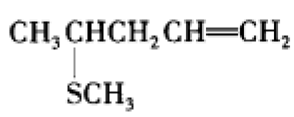
(e) 

(f) 

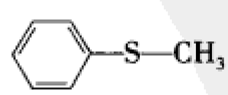
3-11D Names of Sulfides

Sulfur analogs of ethers are called **sulfides** or **thioethers**. They are named by following the same rules used for ethers, with "sulfide" replacing "ether" in the common names. The —SR group is called an alkylthio group. Some examples of sulfides are the following:

dimethyl sulfide
(二甲硫醚)



4-methylthio-1-pentene
(4-甲硫基-1-戊烯)



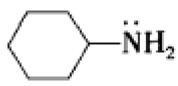
methyl phenyl sulfide
(甲基苯基硫醚)

3-12 Nomenclature of Amines

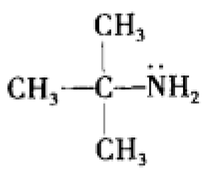
Amines are classified as **primary** (1°), **secondary** (2°), or **tertiary** (3°), corresponding to one, two, or

three alkyl or aryl groups bonded to nitrogen.

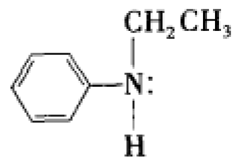
Primary (1°) *amines* (伯胺) *Secondary* (2°) *amines* (仲胺) *Tertiary* (3°) *amines* (叔胺)



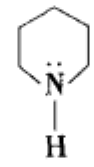
cyclohexylamine (1°) (环己胺)



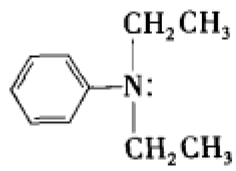
tert-butylamine (1°) (叔丁胺)



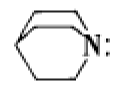
N-ethylaniline (2°) (*N*-乙基苯胺)



piperidine (2°) (哌啶)

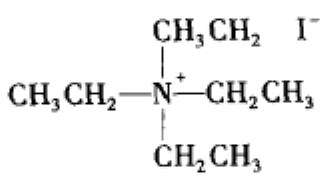


N,*N*-diethylaniline (3°) (*N*,*N*-二乙基苯胺)

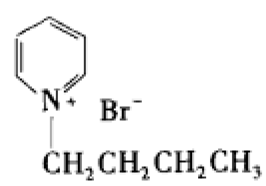


quinuclidine (3°) (奎宁环)

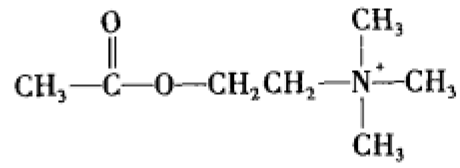
Quaternary ammonium salts have four alkyl or aryl bonds to a nitrogen atom. The nitrogen atom bears a positive charge, just as it does in simple ammonium salts such as ammonium chloride. The following are examples of quaternary (4°) ammonium salts:



tetraethylammonium iodide (四乙基碘化铵)



N-butylpyridinium bromide (*N*-丁基吡啶溴化铵)



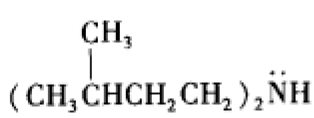
acetylcholine, a neurotransmitter (乙酰胆碱)

3-12A Common Names

Common names of amines are formed from the names of the alkyl groups bonded to nitrogen, followed by the suffix *-amine*. The prefixes *di-*, *tri-*, and *tetra-* are used to describe two, three, or four identical substituents.

$CH_3CH_2\ddot{N}H_2$

ethylamine (乙胺)



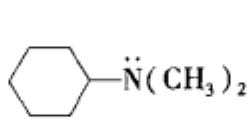
diisopentylamine (二异戊基胺)

$(CH_3CH_2)_2\ddot{N}CH_3$

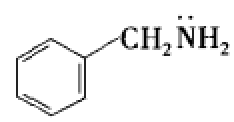
diethylmethylamine (甲基二乙基胺)

$(CH_3CH_2CH_2CH_2)_4N^+\ {}^-Cl$

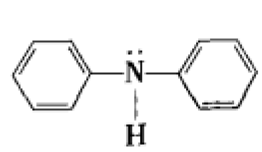
tetrabutylammonium chloride (四丁基氯化铵)



cyclohexyldimethylamine (二甲基环己基胺)

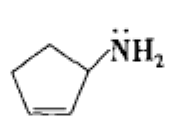


benzylamine (苄胺)

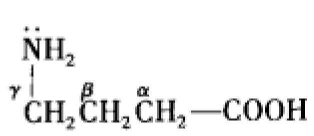


diphenylamine (二苯基胺)

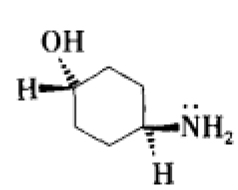
In naming amines with more complicated structures, the $-NH_2$ group is called the **amino** group. It is treated like any other substituent, with a number or other symbol indicating its position on the ring or carbon chain.



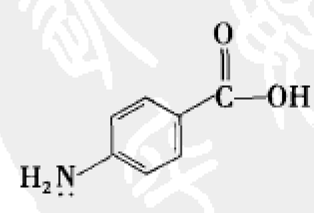
3-aminocyclopentene (3-氨基环戊烯)



γ-aminobutyric acid (4-aminobutanoic acid) (γ-氨基丁酸)

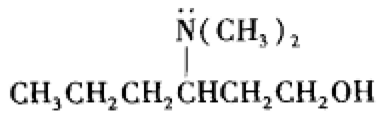


trans-4-aminocyclohexanol (反-4-氨基环己醇)

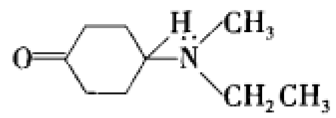


p-aminobenzoic acid (PABA) (对氨基苯甲酸)

Using this system, secondary and tertiary amines are named by classifying the nitrogen atom (together with its alkyl groups) as an alkylamino group. The largest or most complicated alkyl group is taken to be the parent molecule.

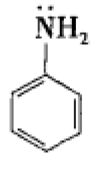


3-dimethylamino-1-hexanol
(3-二甲基氨基-1-己醇)

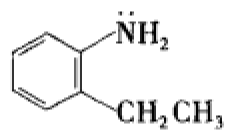


4-(ethylmethylamino)cyclohexanone
[4-(甲基乙基氨基)环己酮]

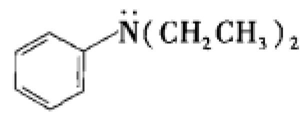
Aromatic and heterocyclic amines are generally known by historical names. Phenylamine is called *aniline*, for example, and its derivatives are named as derivatives of aniline.



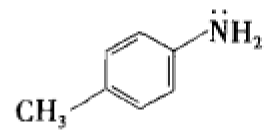
aniline
(苯胺)



2-ethylaniline
(2-乙基苯胺)

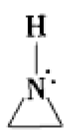


N,*N*-diethylaniline
(*N*,*N*-二乙基苯胺)

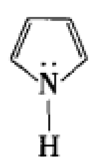


4-methylaniline or *p*-toluidine
(4-甲基苯胺)

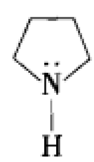
The names and structures of some common nitrogen heterocycles are shown here. The heteroatom is usually assigned position number 1.



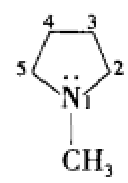
aziridine
(环氮乙烷)



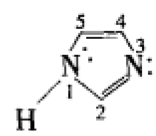
pyrrole
(吡咯)



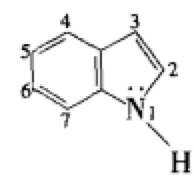
pyrrolidine
(吡咯烷)



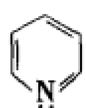
1-methylpyrrolidine
(*N*-methylpyrrolidine)
(*N*-甲基吡咯烷)



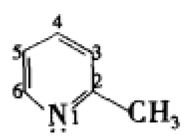
imidazole
(咪唑)



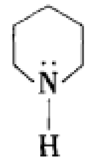
indole
(吲哚)



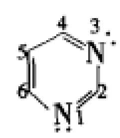
pyridine
(吡啶)



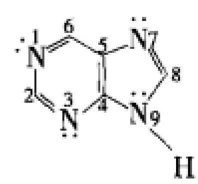
2-methylpyridine
(2-甲基吡啶)



piperidine
(哌啶)



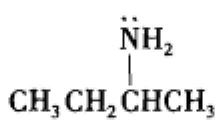
pyrimidine
(嘧啶)



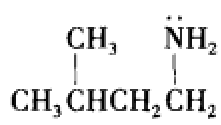
purine
(嘌呤)

3-12B IUPAC Names

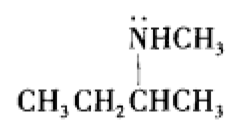
The IUPAC nomenclature for amines is similar to that for alcohols. The longest continuous chain of carbon atoms determines the root name. The *-e* ending in the alkane name is changed to *-amine*, and a number shows the position of the amino group along the chain. Other substituents on the carbon chain are given numbers, and the prefix *N*- is used for each substituent on nitrogen.



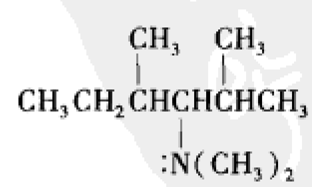
2-butanamine
(2-丁胺)



3-methyl-1-butanamine
(3-甲基-1-丁胺)



N-methyl-2-butanamine
(*N*-甲基-2-丁胺)



2,4,*N*,*N*-tetramethyl-3-hexanamine
(2,4,*N*,*N*-四甲基-3-己胺)

PROBLEM 3-21

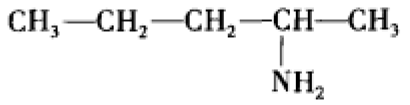
Draw the structures of the following compounds:

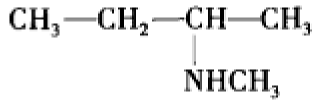
(a) *t*-butylamine
(b) α-aminopropionaldehyde
(c) 4-(dimethylamino)pyridine
(d) 2-methylaziridine

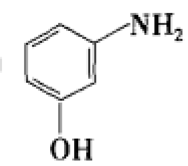
(e) *N*-methyl-*N*-ethyl-3-hexanamine (f) *m*-chloroaniline

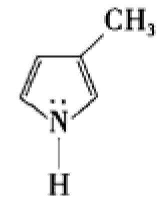
PROBLEM 3−22

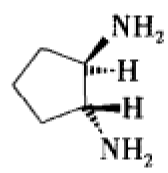
Give correct names for the following amines:

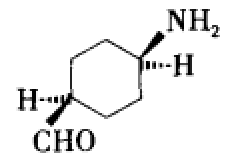
(a) 

(b) 

(c) 

(d) 

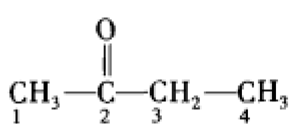
(e) 

(f) 

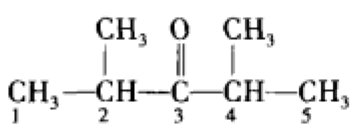
3−13 Nomenclature of Ketones and Aldehydes

3−13A IUPAC Names of Ketones and Aldehydes

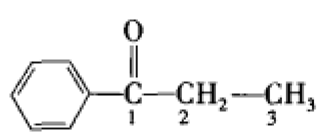
Systematic names of ketones are derived by replacing the final *-e* in the alkane name with *-one*. The "alkane" name becomes "alkanone." In open-chain ketones, we number the longest chain that includes the carbonyl carbon from the end closest to the carbonyl group, and we indicate the position of the carbonyl group by a number. In cyclic ketones, the carbonyl carbon atom is assigned the number 1.



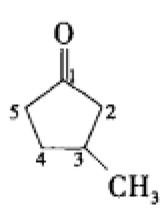
2-butanone
butan-2-one
(2−丁酮)



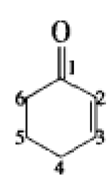
2,4-dimethyl-3-pentanone
2,4-dimethylpentan-3-one
(2,4−二甲基−3−戊酮)



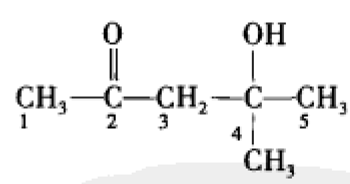
1-phenyl-1-propanone
1-phenylpropan-1-one
(1−苯基−1−丙酮)



3-methylcyclopentanone
(3−甲基环戊酮)

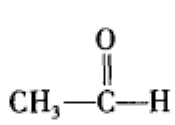


2-cyclohexenone
cyclohex-2-en-1-one
(2−环己烯酮)

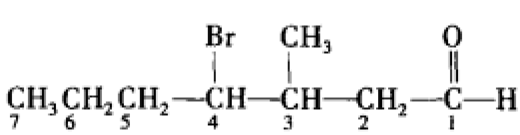


4-hydroxy-4-methyl-2-pentanone
4-hydroxy-4-methylpentan-2-one
(4−甲基−4−羟基−2−环戊酮)

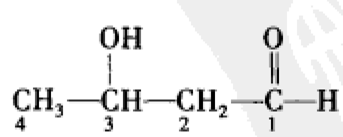
Systematic names for aldehydes are derived by replacing the final *-e* of the alkane name with *-al*. An aldehyde carbon is at the end of a chain, so it is number 1. If the aldehyde group is attached to a large unit (usually a ring), the suffix *carbaldehyde* is used.



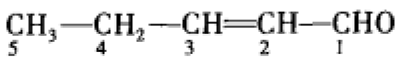
ethanal
(乙醛)



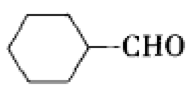
4-bromo-3-methylheptanal
(3−甲基−4−溴庚醛)



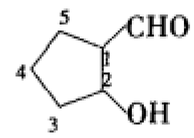
3-hydroxybutanal
(3−羟基丁醛)



2-pentenal
pent-2-enal
(2－戊烯醛)

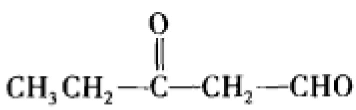


cyclohexanecarbaldehyde
(环己烷甲醛)

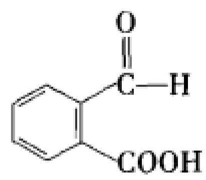


2-hydroxycyclopentane-1-carbaldehyde
(2－羟基环戊烷－1－甲醛)

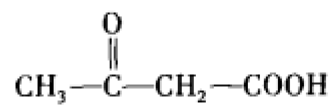
A ketone or aldehyde group can also be named as a substituent on a molecule with another functional group as its root. The ketone carbonyl is designated by the prefix *oxo-*, and the —CHO group is named as a *formyl* group. Carboxylic acids frequently contain ketone or aldehyde groups named as substituents.



3-oxopentanal
(3－氧代戊醛)



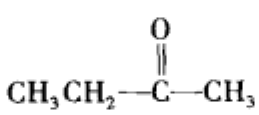
2-formylbenzoic acid
(2－甲酰基苯甲酸)



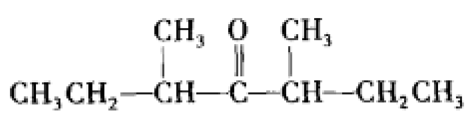
3-oxobutanoic acid
(3－氧代丁酸)

3－13B Common Names of Ketones and Aldehydes

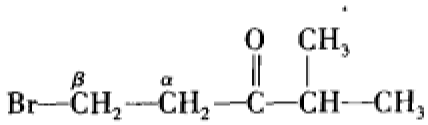
As with other classes of compounds, ketones and aldehydes are often called by common names instead of their systematic IUPAC names. Ketone common names are formed by naming the two alkyl groups bonded to the carbonyl group. Substituent locations are given using Greek letters, beginning with the carbon *next to* the carbonyl group.



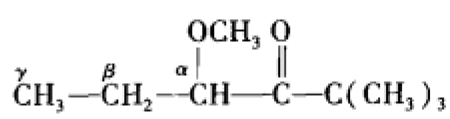
methyl ethyl ketone
(甲基乙基酮)



di-*sec*-butyl ketone
(二仲丁基酮)

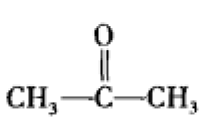


β-bromoethyl isopropyl ketone
(β－溴乙基异丙基酮)

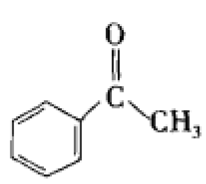


t-butyl α-methoxypropyl ketone
(叔丁基α－甲氧基丙基酮)

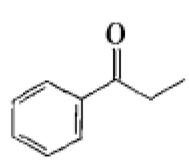
Some ketones have historical common names. Dimethyl ketone is always called *acetone*, and alkyl phenyl ketones are usually named as the acyl group followed by the suffix *-phenone*.



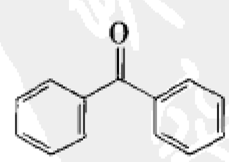
acetone
(丙酮)



acetophenone
(苯乙酮)

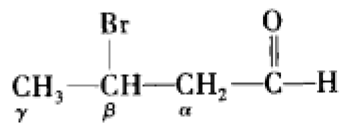


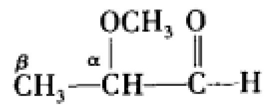
propiophenone
(苯丙酮)



benzophenone
(二苯酮)

Common names of aldehydes are derived from the common names of carboxylic acids (Table 3－4). These names often reflect the Latin or Greek term for the original source of the acid or the aldehyde. Greek letters are used with common names of aldehydes to give the locations of substituents. The first letter (α) is given to the carbon atom *next to* the carbonyl group.





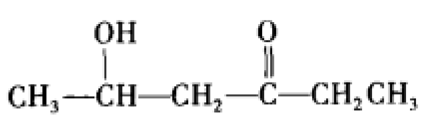
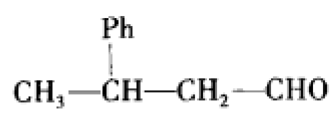
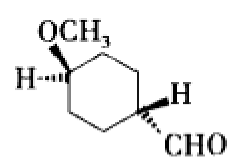
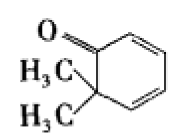
Common name:	β-bromobutyraldehyde	α-methoxypropionaldehyde
IUPAC name:	3-bromobutanal	2-methoxypropanal
	(3-溴代丁醛)	(2-甲氧基丙醛)

TABLE 3-4 Common Names of Aldehydes

IUPAC Name	Common Name	Formula
methanal	formaldehyde (甲醛)	HCHO or CH_2O
ethanal	acetaldehyde (乙醛)	CH_3CHO
propanal	propionaldehyde (丙醛)	CH_3CH_2CHO
butanal	*n*-butyraldehyde (丁醛)	$CH_3(CH_2)_2CHO$
2-methylpropanal	isobutyraldehyde (异丁醛)	$(CH_3)_2CHCHO$
pentanal	*n*-valeraldehyde (戊醛)	$CH_3(CH_2)_3CHO$
3-methylbutanal	isovaleraldehyde (异戊醛)	$(CH_3)_2CHCH_2CHO$
hexanal	caproaldehyde (己醛)	$CH_3(CH_2)_4CHO$
heptanal	*n*-heptaldehyde (庚醛)	$CH_3(CH_2)_5CHO$
propenal	acrolein (丙烯醛)	$CH_2{=}CH{-}CHO$
2-butenal (2-丁烯醛)	crotonaldehyde (巴豆醛)	$CH_3{-}CH{=}CH{-}CHO$
benzaldehyde (苯甲醛)		C_6H_5CHO

PROBLEM 3-23

Give the IUPAC name and (if possible) a common name for each compound.

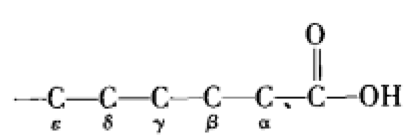
(a)  (b)  (c)  (d) 

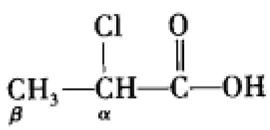
3-14 Nomenclature of Carboxylic Acids

3-14A Common Names

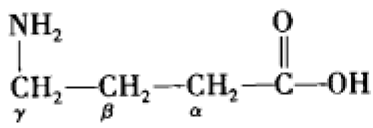
Several aliphatic carboxylic acids have been known for hundreds of years, and their common names reflect their historical sources. *Formic acid* was extracted from ants: *formica* in Latin. Acetic acid was isolated from vinegar, called *acetum* ("sour") in Latin. Propionic acid was considered to be the first fatty acid, and the name is derived from the Greek *protos pion* ("first fat"). Butyric acid results from the oxidation of butyraldehyde, which is found in butter: *butyrum* in Latin. Caproic, caprylic, and capric acids are found in the skin secretions of goats: *caper* in Latin. The names of some carboxylic acids are shown in Table 3-5.

In common names, the positions of substituents are named using Greek letters. Notice that the lettering begins with the carbon atom *adjacent* to the carboxyl carbon, the α carbon. With common names, the prefix *iso-* is sometimes used for acids ending in the $-CH(CH_3)_2$ grouping.

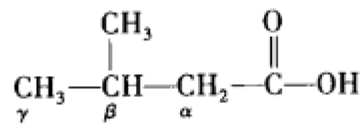




α-chloropropionic acid
(α-氯丙酸)



γ-aminobutyric acid
(γ-氨基丁酸)



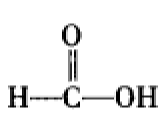
isovaleric acid (β-methylbutyric acid)
(β-甲基丁酸)

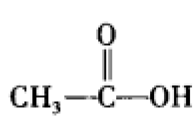
TABLE 3-5 Names of Some Carboxylic Acids

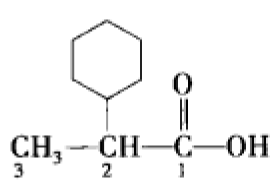
IUPAC Name	Common Name	Formula
methanoic (甲酸)	formic (蚁酸)	$HCOOH$
ethanoic (乙酸)	acetic (醋酸)	CH_3COOH
propanoic (丙酸)	propionic	CH_3CH_2COOH
2-propenoic (2-丙烯酸)	acrylic	$H_2C{=}CH{-}COOH$
butanoic (丁酸)	butyric	$CH_3(CH_2)_2COOH$
2-methylpropanoic (2-甲基丙酸)	isobutyric (异丁酸)	$(CH_3)_2CHCOOH$
trans-2-butenoic (反-2-丁烯酸)	crotonic (巴豆酸)	$CH_3{-}CH{=}CH{-}COOH$
pentanoic (戊酸)	valeric	$CH_3(CH_2)_3COOH$
3-methylbutanoic (3-甲基丁酸)	isovaleric (异戊酸)	$(CH_3)_2CHCH_2COOH$
2,2-dimethylpropanoic (2,2-二甲基丙酸)	pivalic (新戊酸)	$(CH_3)_3C{-}COOH$
hexanoic (己酸)	caproic	$CH_3(CH_2)_4COOH$
octanoic (辛酸)	caprylic	$CH_3(CH_2)_6COOH$
decanoic (癸酸)	capric	$CH_3(CH_2)_8COOH$
dodecanoic (十二酸)	lauric (月桂酸)	$CH_3(CH_2)_{10}COOH$
tetradecanoic (十四酸)	myristic (肉豆蔻酸)	$CH_3(CH_2)_{12}COOH$
hexadecanoic (十六酸)	palmitic (棕榈酸)	$CH_3(CH_2)_{14}COOH$
octadecanoic (十八酸)	stearic (硬脂酸)	$CH_3(CH_2)_{16}COOH$
cis-9-octadecenoic (顺-9-十八烯酸)	oleic (油酸)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
cis,*cis*-9,12-octadecadienoic (顺,顺-9,12-十八二烯酸)	linoleic (亚油酸)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$
cyclohexanecarboxylic (环己烷羧酸)		$c\text{-}C_6H_{11}COOH$
benzoic (苯甲酸)	benzoic (安息香酸)	C_6H_5COOH
2-methylbenzoic (2-甲基苯甲酸)	*o*-toluic (邻甲苯甲酸)	$o\text{-}CH_3C_6H_4COOH$
3-methylbenzoic (3-甲基苯甲酸)	*m*-toluic (间甲苯甲酸)	$m\text{-}CH_3C_6H_4COOH$
4-methylbenzoic (4-甲基苯甲酸)	*p*-toluic (对甲苯甲酸)	$p\text{-}CH_3C_6H_4COOH$

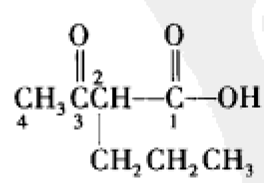
3-14B IUPAC Names

The IUPAC nomenclature for carboxylic acids uses the name of the alkane that corresponds to the longest continuous chain of carbon atoms. The final *-e* in the alkane name is replaced by the suffix *-oic acid*. The chain is numbered, *starting with the carboxyl carbon atom*, to give positions of substituents along the chain. In naming, the carboxyl group takes priority over any of the functional groups discussed previously.

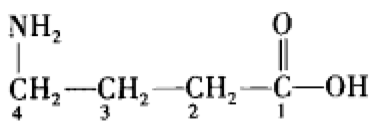
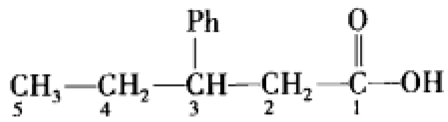
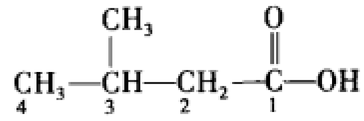




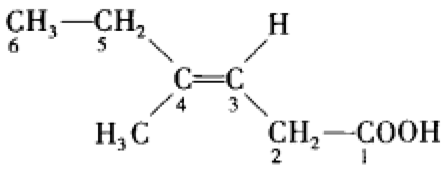
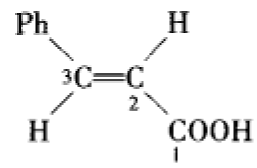
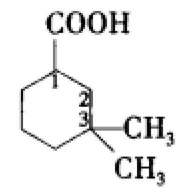




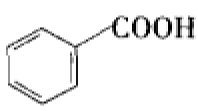
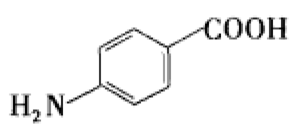
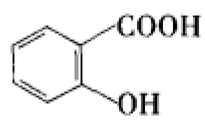
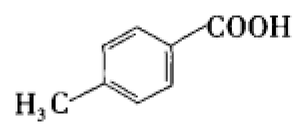
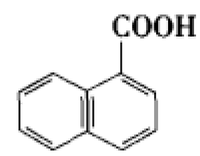
IUPAC name:	methanoic acid	ethanoic acid	2-cyclohexylpropanoic acid	3-*oxo*-2-propylbutanoic acid
common name:	formic acid	acetic acid	α-cyclohexylpropionic acid (α-环己基丙酸)	α-acetylvaleric acid (α-乙酰基戊酸)

			
IUPAC name:	4-aminobutanoic acid	3-phenylpentanoic acid	3-methylbutanoic acid
common name:	γ-aminobutyric acid	β-phenylvaleric acid	isovaleric acid
	(γ-氨基丁酸)	(β-苯基戊酸)	(异戊酸)

Unsaturated acids are named using the name of the corresponding alkene, with the final *-e* replaced by *-oic acid*. The carbon chain is numbered starting with the carboxyl carbon, and a number gives the location of the double bond. The stereochemical terms *cis* and *trans* (and *Z* and *E*) are used as they are with other alkenes. Cycloalkanes with —COOH substituents are generally named as *cycloalkanecarboxylic acids*.

			
IUPAC name:	(*E*)-4-methyl-3-hexenoic acid	*trans*-3-phenyl-2-propenoic acid	3,3-dimethylcyclohexanecarboxylic acid
new IUPAC name:	(*E*)-4-methylhex-3-enoic acid	(*E*)-3-phenylprop-2-enoic acid	
	[(*E*)-4-甲基-3-己烯酸]	(cinnamic acid)(肉桂酸)	(3,3-二甲基环己烷甲酸)

Aromatic acids of the form Ar—COOH are named as derivatives of *benzoic acid*, Ph—COOH. As with other aromatic compounds, the prefixes *ortho-*, *meta-*, and *para-* may be used to give the positions of additional substituents. Numbers are used if there are more than two substituents on the aromatic ring. Many aromatic acids have historical names that are unrelated to their structures.

				
benzoic acid	*p*-aminobenzoic acid	*o*-hydroxybenzoic acid (salicyclic acid)	*p*-methylbenzoic acid (*p*-toluic acid)	α-naphthoic acid
(苯甲酸)	(对氨基苯甲酸)	(邻羟基苯甲酸,水杨酸)	(对甲基苯甲酸)	(α-萘甲酸)

3−14C Nomenclature of Dicarboxylic Acids

Common Names of Dicarboxylic Acids A **dicarboxylic acid** (also called a *diacid*) is a compound with two carboxyl groups. The common names of simple dicarboxylic acids are used more frequently than their systematic names. A common mnemonic for these names is "***O***h ***m***y, ***s***uch ***g***ood ***a***pple ***p***ie," standing for *o*xalic, *m*alonic, *s*uccinic, *g*lutaric, *a*dipic, and *p*imelic acids. The names and physical properties of some dicarboxylic acids are given in Table 3−6.

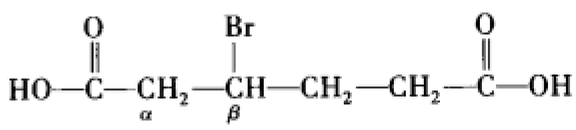
TABLE 3−6 Names of Dicarboxylic Acids

IUPAC Name	Common Name	Formula
ethanedioic (乙二酸)	oxalic (草酸)	HOOC—COOH
propanedioic (丙二酸)	malonic	$HOOCCH_2COOH$
butanedioic (丁二酸)	succinic (琥珀酸)	$HOOC(CH_2)_2COOH$
pentanedioic (戊二酸)	glutaric	$HOOC(CH_2)_3COOH$
hexanedioic (己二酸)	adipic (肥酸)	$HOOC(CH_2)_4COOH$

Continue

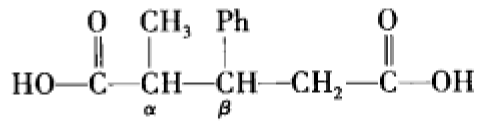
IUPAC Name	Common Name	Formula
heptanedioic（庚二酸）	pimelic	$HOOC(CH_2)_5COOH$
cis-2-butenedioic（顺-2-丁烯二酸）	maleic（马来酸）	*cis*-HOOCCH=CHCOOH
trans-2-butenedioic（反-2-丁烯二酸）	fumaric（富马酸）	*trans*-HOOCCH=CHCOOH
benzene-1,2-dicarboxylic（1,2-苯二甲酸）	phthalic（邻苯二甲酸）	$1,2\text{-}C_6H_4(COOH)_2$
benzene-1,3-dicarboxylic（1,3-苯二甲酸）	isophthalic（间苯二甲酸）	$1,3\text{-}C_6H_4(COOH)_2$
benzene-1,4-dicarboxylic（1,4-苯二甲酸）	terephthalic（对苯二甲酸）	$1,4\text{-}C_6H_4(COOH)_2$

Substituted dicarboxylic acids are given common names using Greek letters, as with the simple carboxylic acids. Greek letters are assigned beginning with the carbon atom adjacent to the carboxyl group that is closer to the substituents.



β-bromoadipic acid

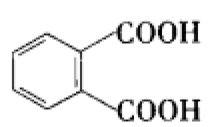
（β-溴己二酸）



α-methyl-β-phenylglutaric acid

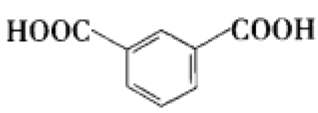
（α-甲基-β-苯基戊二酸）

Benzenoid compounds with two carboxyl groups are named **phthalic acids**. *Phthalic acid* itself is the ortho isomer. The meta isomer is called *isophthalic acid*, and the *para* isomer is called *terephthalic acid*.



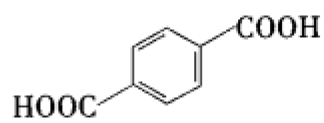
o-phthalic acid（邻苯二甲酸）

phthalic acid



m-phthalic acid（间苯二甲酸）

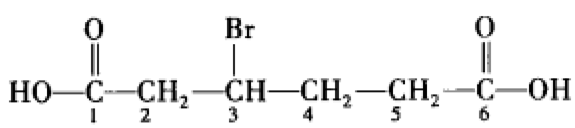
isophthalic acid



p-phthalic acid（对苯二甲酸）

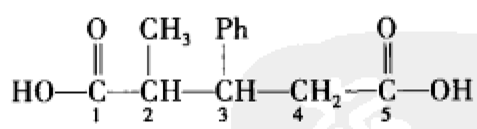
terephthalic acid

IUPAC Names of Dicarboxylic Acids Aliphatic dicarboxylic acids are named simply by adding the suffix *-dioic acid* to the name of the parent alkane. For straight-chain dicarboxylic acids, the parent alkane name is determined by using the longest continuous chain that contains both carboxyl groups. The chain is numbered beginning with the carboxyl carbon atom that is closer to the substituents, and these numbers are used to give the positions of the substituents.



3-bromohexanedioic acid

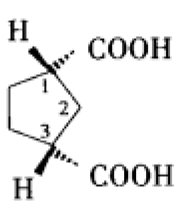
（3-溴己二酸）



2-methyl-3-phenylpentanedioic acid

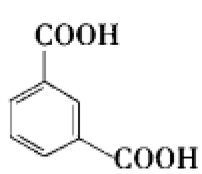
（2-甲基-3-苯基戊二酸）

The system for naming cyclic dicarboxylic acids treats the carboxyl groups as substituents on the cyclic structure.



cis-1,3-cyclopentanedicarboxylic acid

（顺-1,3-环戊烷二羧酸）



1,3-benzenedicarboxylic acid

（1,3-苯二羧酸）

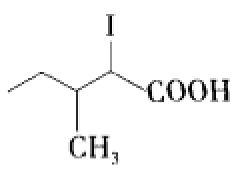
PROBLEM 3−24

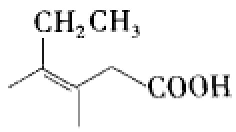
Draw the structures of the following carboxylic acids.

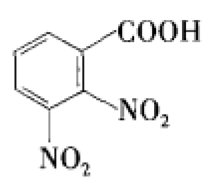
(a) α-methylbutyric acid
(b) 2-bromobutanoic acid
(c) 4-aminopentanoic acid
(d) *cis*-4-phenyl-2-butenoic acid
(e) *trans*-2-methylcyclohexanecarboxylic acid
(f) 2,3-dimethylfumaric acid
(g) *m*-chlorobenzoic acid
(h) 3-methylphthalic acid
(i) β-aminoadipic acid
(j) 3-chloroheptanedioic acid
(k) 4-oxoheptanoic acid
(l) phenylacetic acid

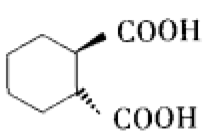
PROBLEM 3−25

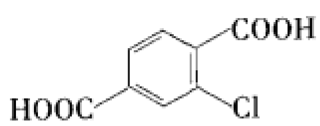
Name the following carboxylic acids (when possible, give both a common name and a systematic name).

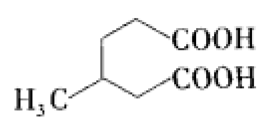
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

3−15 Structure and Nomenclature of Acid Derivatives

3−15A Esters and Salts of Carboxylic Acids

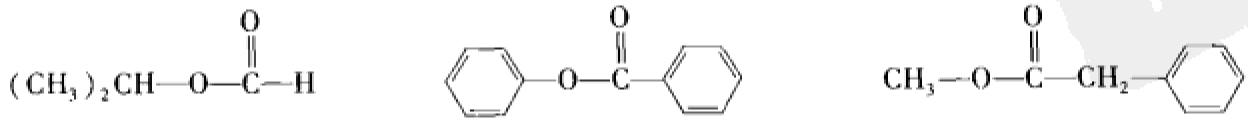
Esters are carboxylic acid derivatives in which the hydroxyl group (—OH) is replaced by an alkoxy group (—OR). An ester is a combination of a carboxylic acid and an alcohol, with loss of a molecule of water.

$$\underset{\text{acid}}{R-\overset{O}{\overset{\|}{C}}-OH} + \underset{\text{alcohol}}{R'-OH} \overset{H^+}{\rightleftharpoons} \underset{\text{ester}}{R-\overset{O}{\overset{\|}{C}}-O-R'} + H_2O$$

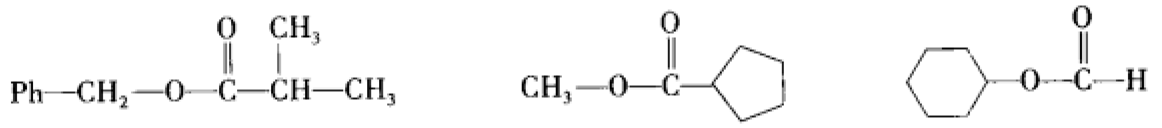
The names of esters consist of two words that reflect their composite structure. The first word is derived from the *alkyl* group of the alcohol, and the second word from the *carboxylate* group of the carboxylic acid. The IUPAC name is derived from the IUPAC names of the alkyl group and the carboxylate, and the common name is derived from the common names of each. The following examples show both the IUPAC names and the common names of some esters:

$$CH_3CH_2-OH + HO-\overset{O}{\overset{\|}{C}}-CH_3 \overset{H^+}{\rightleftharpoons} CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3 + H_2O$$

IUPAC name: ethanol; ethanoic acid; ethyl ethanoate
common name: ethyl alcohol (乙醇); acetic acid (乙酸); ethyl acetate (乙酸乙酯)

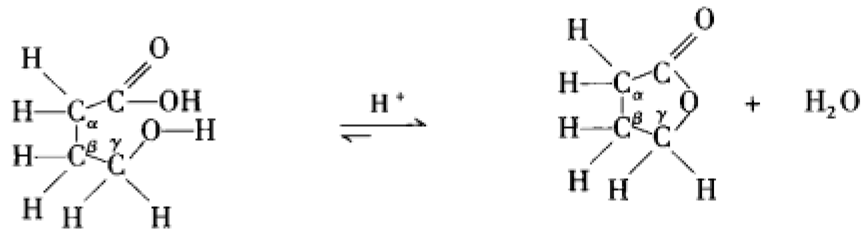


IUPAC name:	1-methylethyl methanoate	phenyl benzoate	methyl 2-phenylethanoate
common name:	isopropyl formate (甲酸异丙酯)	phenyl benzoate (苯甲酸苯酯)	methyl phenylacetate (苯基乙酸甲酯)



IUPAC name:	benzyl 2-methylpropanoate	methyl cyclopentanecarboxylate	cyclohexyl methanoate
common name:	benzyl isobutyrate	methyl cyclopentanecarboxylate	cyclohexyl formate
	(异丁酸苄酯)	(环戊烷羧酸甲酯)	(甲酸环己酯)

Lactones Cyclic esters are called **lactones**. A lactone is formed from an open-chain hydroxy acid in which the hydroxyl group has reacted with the acid group to form an ester.



IUPAC name:	4-hydroxybutanoic acid	4-hydroxybutanoic acid lactone (4-羟基丁酸内酯)
common name:	γ-hydroxybutyric acid	γ-butyrolactone
	(γ-羟基丁酸)	(γ-丁内酯)

The IUPAC names of lactones are derived by adding the term *lactone* at the end of the name of the parent acid. The common names of lactones, used more often than IUPAC names, are formed by changing the *-ic acid* ending of the hydroxy acid to *-olactone*. A Greek letter designates the carbon atom that bears the hydroxy group to close the ring. Substituents are named just as they are on the parent acid.

IUPAC name:	5-hydroxypentanoic acid lactone	4-hydroxy-2-methylpentanoic acid lactone
	(5-羟基戊酸内酯)	(2-甲基-4-羟基戊酸内酯)
common name:	δ-valerolactone	α-methyl-γ-valerolactone
	(δ-戊内酯)	(α-甲基-γ-戊内酯)

Carboxylic Acid Salts Salts of carboxylic acids are named simply by naming the cation, then naming the carboxylate ion by replacing the *-ic acid* part of the acid name with *-ate*. The following examples show the formation and nomenclature of some salts:

$$CH_3CH_2CH_2CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH \quad + \quad LiOH \longrightarrow CH_3CH_2CH_2CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-O^{-}\,{}^{+}Li$$

IUPAC name:	pentanoic acid	lithium hydroxide	lithium pentanoate
common name:	valeric acid		lithium valerate
	(戊酸)	(氢氧化锂)	(戊酸锂)

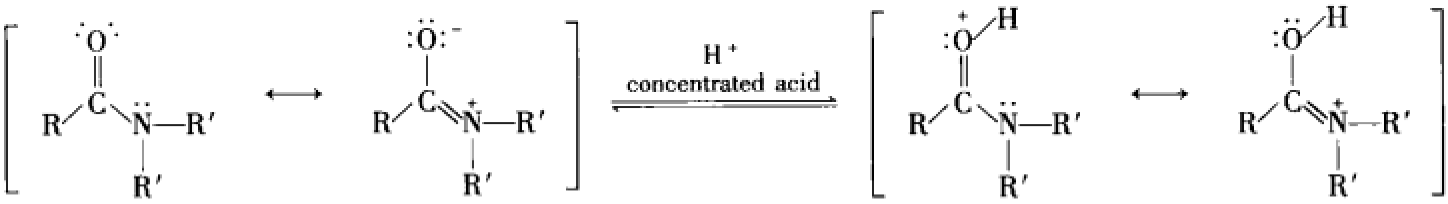
$$CH_3CH_2CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH \quad + \ :NH_3 \longrightarrow CH_3CH_2CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-O^{-}\,{}^{+}NH_4$$

IUPAC name:	butanoic acid	ammonia	ammonium butanoate
common name:	butyric acid		ammonium butyrate
	(丁酸)	(氨)	(丁酸铵)

3-15B Amides

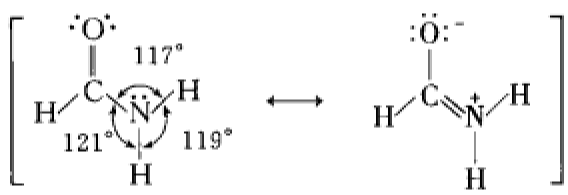
An **amide** is a composite of a carboxylic acid and ammonia or an amine. The simple amide structure shows a nonbonding pair of electrons on the nitrogen atom. Unlike amines, however, amides are only weakly basic, and

we consider the amide functional group to be neutral. A concentrated strong acid is required to protonate an amide, and protonation occurs on the carbonyl oxygen atom rather than on nitrogen. This lack of basicity can be explained by picturing the amide as a resonance hybrid of the conventional structure and a structure with a double bond between carbon and nitrogen.



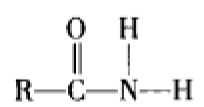
very weakly basic protonation on oxygen

This resonance representation correctly predicts a planar amide nitrogen atom that is sp^2 hybridized to allow pi bonding with the carbonyl carbon atom. For example, formamide has a planar structure like an alkene. The C—N bond has partial double-bond character, with a rotational barrier of 75 kJ/mol.

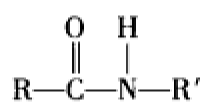


formamide (甲酰胺)

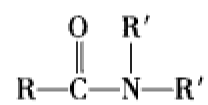
An amide of the form R—CO—NH_2 is called a **primary amide** because there is only one carbon atom bonded to the amide nitrogen. An amide with an alkyl group on nitrogen (R—CO—NHR′) is called a **secondary amide** or an ***N*-substituted amide**. Amides with two alkyl groups on the amide nitrogen (R—CO—NR'_2) are called **tertiary amides** or ***N*,*N*-disubstituted amides**.



primary amide (伯酰胺)

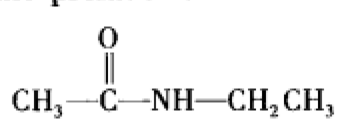
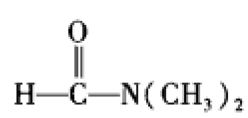
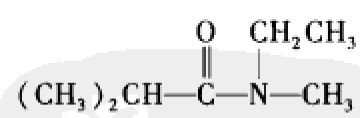


secondary amide (仲酰胺)
(*N*-substituted amide)

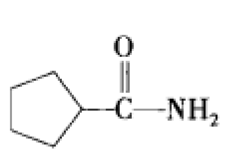


tertiary amide (叔酰胺)
(*N*,*N*-disubstituted amide)

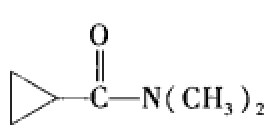
To name a primary amide, first name the corresponding acid. Drop the *-ic acid* or *-oic acid* suffix, and add the suffix *-amide*. For secondary and tertiary amides, treat the alkyl groups on nitrogen as substituents, and specify their position by the prefix *N*-.

			
IUPAC name:	*N*-ethylethanamide	*N*,*N*-dimethylmethanamide	*N*-ethyl-*N*,2-dimethylpropanamide
common name:	*N*-ethylacetamide	*N*,*N*-dimethylformamide	*N*-ethyl-*N*-methylisobutyramide
	(*N*-乙基乙酰胺)	(*N*,*N*-二甲基甲酰胺)	(*N*-甲基-*N*-乙基异丁酰胺)

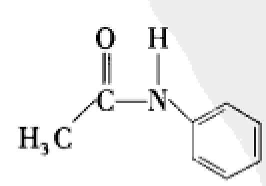
For acids that are named as alkanecarboxylic acids, the amides are named by using the suffix *-carboxamide*. Some amides, such as acetanilide, have historical names that are still commonly used.



cyclopentanecarboxamide
(环戊烷甲酰胺)



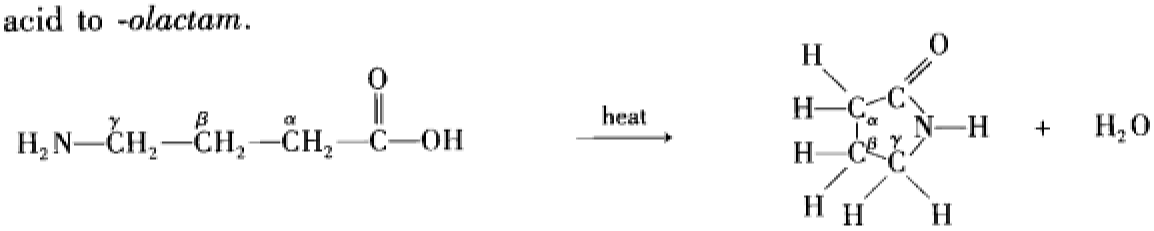
N,*N*-dimethylcyclopropanecarboxamide
(*N*,*N*-二甲基环丙烷甲酰胺)



acetanilide
(乙酰苯胺)

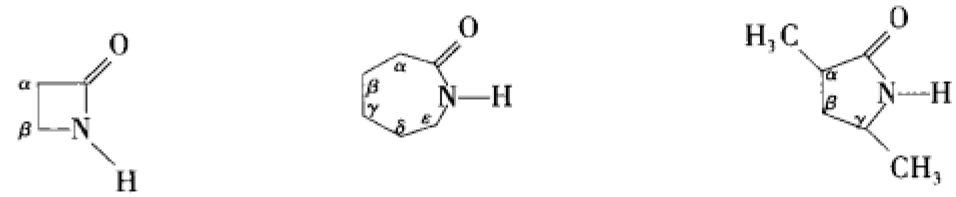
Lactams Cyclic amides are called **lactams**. Lactams are formed from amino acids, where the amino group and the carboxyl group have joined to form an amide. Lactams are named like lactones, by adding the term *lactam* at

the end of the IUPAC name of the parent acid. Common names of lactams are formed by changing the *-ic acid* ending of the amino acid to *-olactam*.



IUPAC name: 4-aminobutanoic acid (4−氨基丁酸) → 4-aminobutanoic acid lactam (4−氨基丁酸内酰胺)

common name: γ-aminobutyric acid (γ−氨基丁酸) → γ-butyrolactam (γ−丁内酰胺)

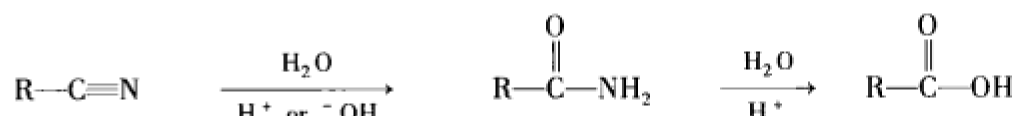


IUPAC name:	3-aminopropanoic acid lactam (3−氨基丙酸内酰胺)	6-aminohexanoic acid lactam (6−氨基己酸内酰胺)	4-amino-2-methylpentanoic acid lactam (2−甲基−4−氨基戊酸内酰胺)
common name:	β-propiolactam (β−丙内酰胺)	ε-caprolactam (ε−己内酰胺)	α-methyl-γ-valerolactam (α−甲基−γ−戊内酰胺)

3−15C Nitriles

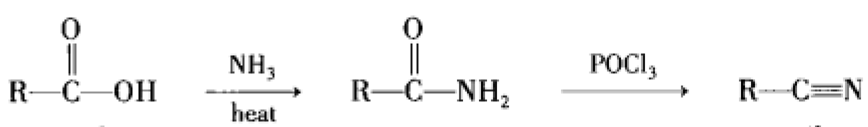
Nitriles contain the **cyano group**, —C≡N. Although nitriles lack the carbonyl group of carboxylic acids, they are classified as acid derivatives because they hydrolyze to give carboxylic acids and can be synthesized by dehydration of amides.

Hydrolysis to an acid



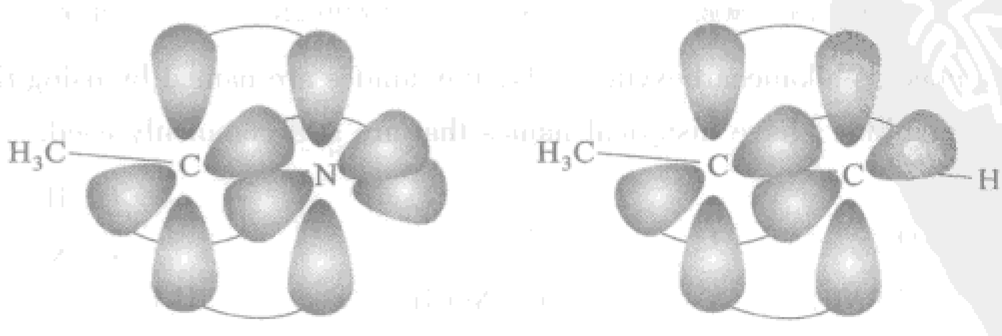
nitrile (腈) → primary amide (伯酰胺) → acid

Synthesis from an acid



acid → primary amide → nitrile

Both the carbon atom and the nitrogen atom are *sp* hybridized, and the R—C≡N bond angle is 180° (linear). The structure of a nitrile is similar to that of a terminal alkyne, except that the nitrogen atom of the nitrile has a lone pair of electrons in place of the acetylenic hydrogen of the alkyne. Figure 3−5 compares the structures of acetonitrile and propyne.



acetonitrile (乙腈) propyne (丙炔)

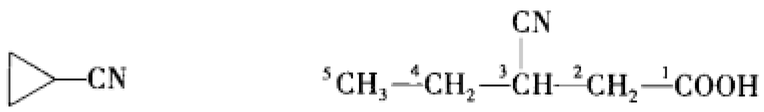
Figure 3−5 Comparison of the electronic structures of acetonitrile and propyne (methylacetylene). In both compounds, the atoms at the ends of the triple bonds are *sp* hybridized, and the bond angles are 180°. In place of the acetylenic hydrogen atom, the nitrile has a lone pair of electrons in the *sp* orbital of nitrogen.

Although a nitrile has a lone pair of electrons on nitrogen, it is not very basic. A typical nitrile has a pK_b of about 24, requiring a concentrated solution of mineral acid to protonate the nitrile. We explain this lack of basicity by noting that the nitrile's lone pair resides in an *sp*-hybrid orbital, with 50% *s* character. This orbital is close to the nucleus, and these electrons are tightly bound and relatively unreactive.

Nitrile nomenclature is derived from that of carboxylic acids. The IUPAC name is constructed from the alkane name, with the suffix *-nitrile* added. For common names, the suffix *-ic acid* is replaced by the suffix *-onitrile*.

IUPAC name:	ethanenitrile	3-bromobutanenitrile	5-methoxyhexanenitrile
common name:	acetonitrile (乙腈)	β-bromobutyronitrile (β-溴丁腈)	δ-methoxycapronitrile (δ-甲氧基己腈)

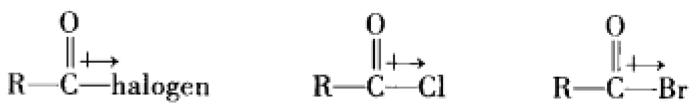
For acids that are named as alkanecarboxylic acids, the corresponding nitriles are named by using the suffix-*carbonitrile*. The —C≡N group can also be named as a substituent, the *cyano group*.



cyclopropanecarbonitrile (环丙烷甲腈)　　3-cyanopentanoic acid (3-氰基戊酸)

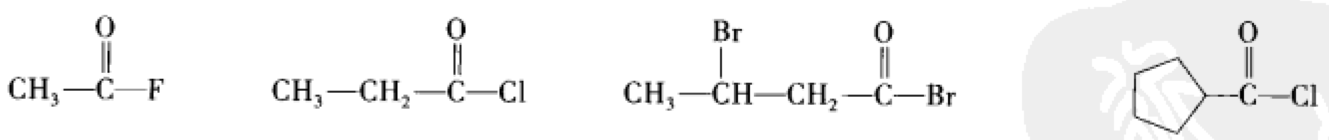
3-15D Acid Halides

Acid halides, also called **acyl halides**, are activated derivatives used for the synthesis of other acyl compounds such as esters, amides, and acylbenzenes. The most common acyl halides are the acyl chlorides (acid chlorides), and we will generally use acid chlorides as examples.



an acid halide	acid chloride	acid bromide
(acyl halide)	(acyl chloride)	(acyl bromide)
(酰卤)	(酰氯)	(酰溴)

An acid halide is named by replacing the *-ic acid* suffix of the acid name with *-yl* and the halide name. For acids that are named as alkanecarboxylic acids, the acid chlorides are named by using the suffix *-carbonyl chloride*.

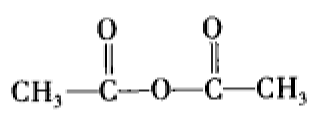


ethanoyl fluoride	propanoyl chloride	3-bromobutanoyl bromide	cyclopentanecarbonyl chloride
acetyl fluoride	propionyl chloride	β-bromobutyryl bromide	
(乙酰氟)	(丙酰氯)	(β-溴丁酰溴)	(环戊烷甲酰氯)

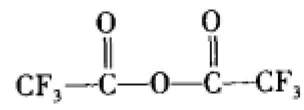
3-15E Acid Anhydrides

The word **anhydride** means "without water." An acid anhydride contains two molecules of an acid, with loss of a molecule of water. Diacids commonly form cyclic anhydrides, especially if a five-or six-membered ring results.

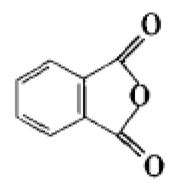
Anhydride nomenclature is very simple; the word *acid* is changed to *anhydride* in both the common name and the IUPAC name (rarely used). The following examples show the names of some common anhydrides:



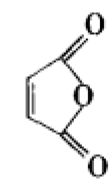
(abbreviated Ac_2O)
ethanoic anhydride
acetic anhydride (乙酸酐)



(abbreviated TFAA)
trifluoroethanoic anhydride
trifluoroacetic anhydride (三氟乙酸酐)

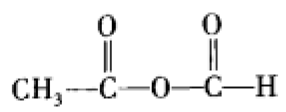


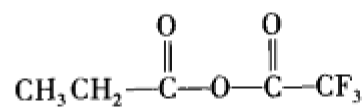
1,2-benzenedicarboxylic anhydride
phthalic anhydride (邻苯二甲酸酐)



but-2-enedioic anhydride
maleic anhydride (马来酸酐)

Anhydrides composed of two different acids are called **mixed anhydrides** and are named by using the names of the individual acids.





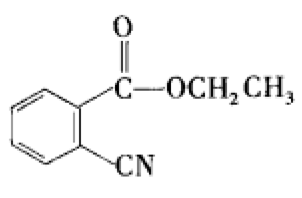
IUPAC name:	ethanoic methanoic anhydride	trifluoroethanoic propanoic anhydride
common name:	acetic formic anhydride (甲酸乙酸酐)	trifluoroacetic propionic anhydride (三氟乙酸丙酸酐)

3-15F Nomenclature of Multifunctional Compounds

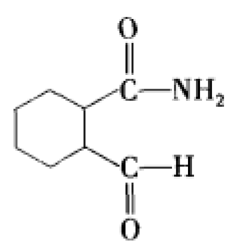
With all the different functional groups we have studied, it is not always obvious which functional group of a multifunctional compound is the "main" one and which groups should be named as substituents. In choosing the principal group for the root name, we use the following priorities:

acid > ester > amide > nitrile > aldehyde > ketone > alcohol > amine > alkene > alkyne

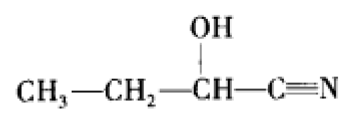
The following examples illustrate the priorities in naming multifunctional compounds (see Table 3-3):



ethyl *o*-cyanobenzoate
(邻氰基苯甲酸乙酯)



2-formylcyclohexanecarboxamide
(2-甲酰基环己烷甲酰胺)



2-hydroxybutanenitrile
(2-羟基丁腈)

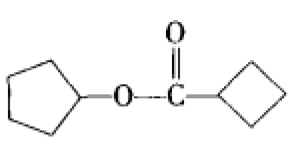
PROBLEM 3-26

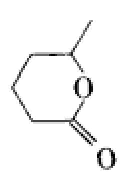
Name the following carboxylic acid derivatives, giving both a common name and an IUPAC name where possible.

(a) $PhCOOCH_2CH(CH_3)_2$ (b) PhOCHO (c) $PhCH(CH_3)COOCH_3$

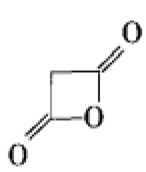
(d) $PhNHCOCH_2CH(CH_3)_2$ (e) $CH_3CONHCH_2Ph$ (f) $CH_3CH(OH)CH_2CN$

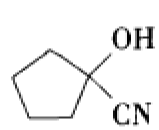
(g) $(CH_3)_2CHCH_2COBr$ (h) $Cl_2CHCOCl$ (i) $(CH_3)_2CHCOOCHO$

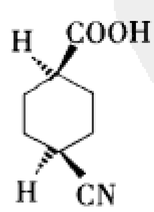
(j) 

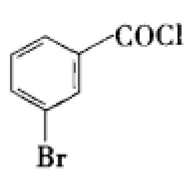
(k) 

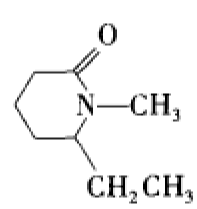
(l)

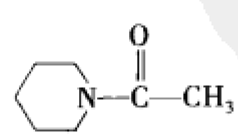
(m) 

(n) 

(o) 

(p) 

(q) 

(r) 

(*Hint*: Named as a piperidine derivative.)

Summary in Chinese

本 章 概 要

一、烷烃命名规则要点

1. 选择取代基多的最长碳链为主链。

2. 从距取代基最近的一端开始，将主链中的碳原子依次编号；编号遵循“最低系列原则”，即将主链分别从两端编号，考虑在两种编号系列中出现的第一组不同编号，编号小的定为“最低系列”；在两种编号系列相同的情况下，给命名中首先写出的取代基尽可能低的位次编号。

3. 当母体链上有两个或两个以上取代基，用英文命名时，取代基的名称按英文26个字母顺序列出；当有两个或两个以上相同取代基时，用“di-，tri-，tetra-”等词头表示相同取代基的个数。[提示：用中文命名时，取代基的名称按原子或基团的“优先规则”，即Cahn-Ingold-Prelog规则（Section 3-5C）列出，优先性低的原子或基团在中文名称中先列出]。

4. 如侧链上还有取代基，则从与主链相连的碳原子开始，给侧链的碳原子依次编号，确定侧链上取代基的位置。

二、烯烃和炔烃的命名规则要点

1. 选择含双键、三键多的最长碳链为主链；在双键和三键数目相同，并且碳链长度也相同的情况下，选择含双键最多的碳链为主链。

2. 给双键或三键尽可能低的位次编号，如双键和三键在主链上处于同等位置，优先考虑双键，给其最低位次。

三、官能团化合物命名规则要点

1. 按官能团优先顺序（见Table 3-3）选择化合物中优先顺序最高的官能团作为主要官能团，按此类官能团化合物命名，其他排序低的官能团命名为取代基。

2. 选择带有主要官能团、取代基多的最长碳链为主链，从距官能团最近的一端开始给主链碳原子编号，其他命名规则与烷烃相同。

四、常见有机化合物中英文系统命名一览表（化合物官能团按优先性自上而下降低的顺序排列）。

分子通式	分类名	官能团	作为主要官能团命名[a]	作为取代基命名
R—C(=O)—OH	carboxylic acid （羧酸）	—C(=O)—OH	-oic acid（－酸） -carboxylic acid[b]（－羧酸）	carboxy （羧基）
R—C(=O)—OM	carboxylic acid salts （羧酸盐）	—C(=O)—OM	-oate（－酸盐） -carboxylate[b]（－羧酸盐）	
R—C(=O)—O—C(=O)—R	acid anhydrides （酸酐）	—C(=O)—O—C(=O)—	-oic anhydride（－酸酐） -carboxylate anhydride[b]（－羧酸酐，－甲酸酐）	
R—C(=O)—OR′	esters （酯）	—C(=O)—OR′	-oate（－酯） -carboxylate[b]（－羧酸酯）	alkoxycarbonyl （烷氧基酰基，酯基）
R—C(=O)—X	acid halides or acyl halides （酰卤）	—C(=O)—X	-oyl halide（－酰卤） -carbonyl halide[b]（－甲酰卤）	haloformyl （卤代甲酰基）
R—C(=O)—NH$_2$	amides （酰胺）	—C(=O)—NH$_2$	-amide（－酰胺） -carboxamide[b]（－甲酰胺）[c]	carbamoyl （氨基甲酰基）
R—C≡N	nitriles （腈）	—C≡N	-nitrile（－腈） -carbonitrile[b]（－甲腈）	cyano （氰基）
R—C(=O)—H	aldehydes （醛）	—C(=O)—H	-al（－醛） -carbaldehyde[b]（－甲醛）	formyl （甲酰基）
R—C(=O)—R′	ketones （酮）	>C=O	-one（－酮）	oxo[d] （氧代）
R—OH	alcohols （醇）	—OH	-ol（－醇）	hydroxyl （羟基）
R—SH	thiols （硫醇）	—SH	-thiol（－硫醇） [俗名：R（基团名）+ mercaptan]	mercapto （巯基）
R—NH$_2$	amines （胺）	—NH$_2$	-amine（－胺）	amino （氨基）

续表

分子通式	分类名	官能团	作为主要官能团命名[a]	作为取代基命名
$RR^1C{=}CR^2R^3$	alkenes（烯烃）	$>C{=}C<$	-ene（－烯）	alkenyl（烯基）
R—C≡C—R′	alkynes（炔烃）	—C≡C—	-yne（－炔）	alkynyl（炔基）
R—H	alkanes（烷烃）		-ane（－烷）	alkyl（烷基）
R—O—R′	ethers（醚）	—OR′	（俗名：R，R′基团名 + ether）	alkoxy（烷氧基）
R—S—R′	Sulfides or thioethers（硫醚）	—SR′	（俗名：R，R′基团名 + sulfide）	alkylthio（烷硫基）
$R—NO_2$	nitroalkane（硝基烷烃）	$—NO_2$		nitro（硝基）
R—X	halides（卤代烃）	—X	［俗名：R（基团名）+ halide，仅用于 C_4 或 C_4 以下卤代烃］	halo（fluoro，chloro，bromo，iodo）（卤代）

[a] 如官能团词尾为元音开头时，删去烃类母体名中词尾-ane，-ene，-yne 最后一个字母"e"，再加官能团词尾；如官能团词尾为辅音，则保留烃类母体名词尾不变，直接加官能团词尾。

[b] 当母体名中未包含羰基碳原子时，使用该词尾。

[c] 如 $—CONH_2$ 英文名为 cyclopropanecarboxamide，中文可命名为环丙基甲酰胺。

[d] 酮的官能团为羰基（$>C{=}O$），英文名为 carbonyl，当酮的官能团作为取代基命名时，因羰基碳原子已包括在母体名中，只命名双键键合的氧原子，称为氧代（oxo）。

Essential Problem-Solving Skills in Chapter 3

1. Correctly draw and name alkanes, alkenes, and alkynes with a given molecular formula.
2. Identify and draw cis-trans stereoisomers of alkenes and cycloalkanes.
3. Use the *E-Z* and cis-trans systems to name geometric isomers of alkenes.
4. Name aromatic compounds, and draw their structures from the names.
5. Correctly name alkyl halides, and identify them as 1°, 2°, or 3°.
6. Name alcohols, ethers including epoxides and heterocyclic ethers, thiols, and sulfides, and draw the structures from their names.
7. Name amines, draw the structures from their names, and identify them as 1°, 2°, or 3°.
8. Name ketones, aldehydes, and draw structures from their names.
9. Name carboxylic acids and their derivatives, and draw the structures from their names.
10. Name and draw aromatic heterocyclic compounds given in Chapter 3.

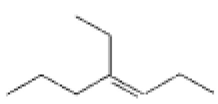
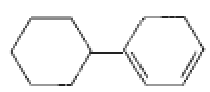
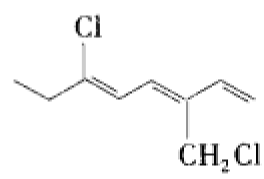
Study Problems

3-27 Draw the structure that corresponds with each name.

(a) 3-ethyloctane (b) 4-isopropyldecane (c) *sec*-butylcycloheptane
(d) 2,3-dimethyl-4-propylnonane (e) 2,2,4,4-tetramethylhexane (f) *trans*-1,3-diethylcyclopentane
(g) *cis*-1-ethyl-4-methylcyclohexane (h) isobutylcyclopentane (i) *t*-butylcyclohexane
(j) pentylcyclohexane (k) cyclobutylcyclohexane (l) *cis*-1-bromo-3-chlorocyclohexane

3-28 Give a correct name for each compound.

(a) $CH_3—CH_2—C(=CH_2)—CH_2—CH_2—CH_3$ (b) $(CH_3CH_2)_2C{=}CHCH_3$ (c)

(d)  (e)  (f) 

3-29 Determine which compounds show cis-trans isomerism. Draw and label the isomers, using both the cis-trans and *E-Z* nomenclatures where applicable.

(a) 1-pentene (b) 2-pentene (c) 3-hexene
(d) 1,1-dibromopropene (e) 1,2-dibromopropene (f) hexa-2,4-diene

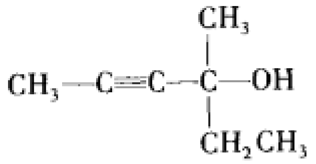
3-30 Write structural formulas for the following compounds.

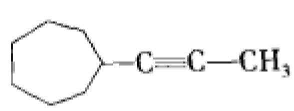
(a) 3-nonyne (b) methyl-*n*-pentylacetylene (c) ethynylbenzene
(d) cyclohexylacetylene (e) 5-methyl-3-octyne (f) *trans*-3,5-dibromocyclodecyne
(g) 3-octyn-2-ol (h) *cis*-6-ethyl-2-octen-4-yne (i) 1,4-heptadiyne
(j) vinylacetylene (k) (*S*)-3-methyl-1-penten-4-yne

3-31 Give IUPAC names for the following compounds.

(a) $CH_3—C{\equiv}C—CH(Ph)—CH_3$ (b) $CH_3—CBr_2—C{\equiv}C—CH_3$

(c) $(CH_3)_2CH—C{\equiv}C—CH_2C(CH_3)_3$ (d) $CH_3CH_2—C{\equiv}C—C(CH_3){=}C(H)—CH_3$

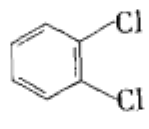
(e) 

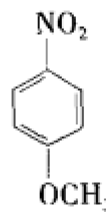
(f) 

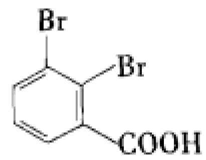
3-32 Draw the structure of each compound.

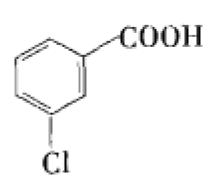
(a) *o*-nitroanisole
(b) 2,4-dimethoxyphenol
(c) *p*-aminobenzoic acid
(d) 4-nitroaniline
(e) *m*-chlorotoluene
(f) *p*-divinylbenzene
(g) *p*-bromostyrene
(h) 3,5-dimethoxybenzaldehyde
(i) sodium cyclopentadienide
(j) 2-phenylpropan-1-ol
(k) benzyl methyl ether
(l) *p*-toluenesulfonic acid
(m) *o*-xylene
(n) 3-benzylpyridine

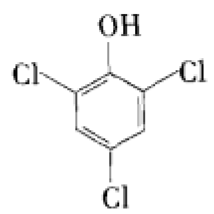
3-33 Name the following compounds:

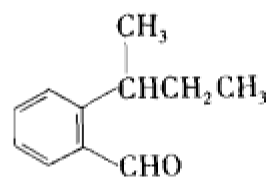
(a) 

(b) 

(c) 

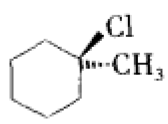
(d) 

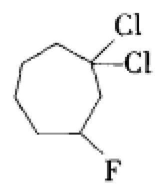
(e) 

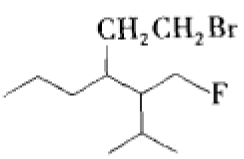
(f) 

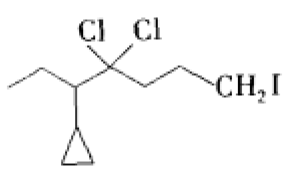
3-34 Give systematic (IUPAC) names for the following compounds.

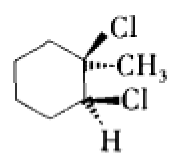
(a)

(b) 

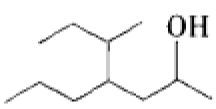
(c) 

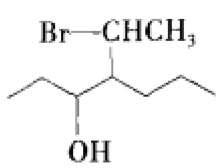
(d) 

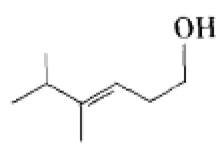
(e) 

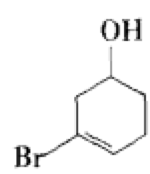
(f) 

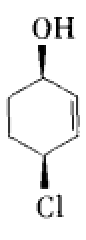
3-35 Give a systematic (IUPAC) name for each alcohol. Classify each as primary, secondary, or tertiary.

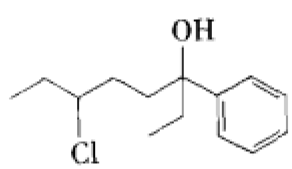
(a) 

(b) 

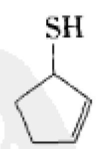
(c) 

(d) 

(e) 

(f) 

(g)

(h) 

3-36 Draw the structures of the following compounds.

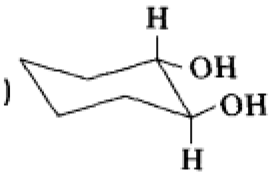
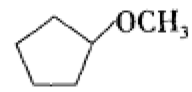
(a) triphenylmethanol
(b) 3-(bromomethyl)-4-octanol
(c) 3-cyclopenten-1-ol
(d) 3-cyclohexylpentan-3-ol
(e) *meso*-2,4-pentanediol
(f) cyclopentene glycol
(g) 4-iodophenol
(h) (2*R*,3*R*)-2,3-hexanediol
(i) cyclopentene-3-thiol
(j) dimethyl disulfide
(k) 3-methylhex-4-yne-2-ol

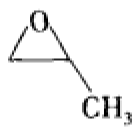
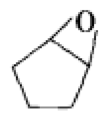
3-37 Write structural formulas for the following compounds.

(a) ethyl isopropyl ether
(b) di-*n*-butyl ether
(c) 2-ethoxyoctane
(d) divinyl ether
(e) allyl methyl ether
(f) cyclohexene oxide
(g) *cis*-2,3-epoxyhexane
(h) *trans*-2,3-dimethyloxirane

3−38 Give common names for the following compounds.

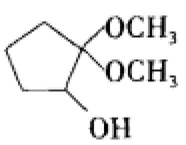
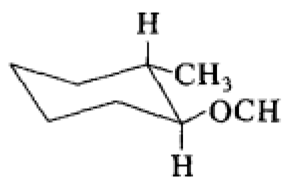
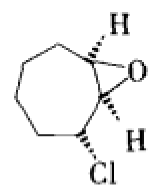
(a) $(CH_3)_2CH—O—CH(CH_3)CH_2CH_3$ (b) $(CH_3)_3C—O—CH_2CH(CH_3)_2$ (c) $Ph—O—CH_2CH_3$

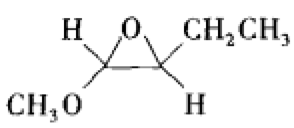
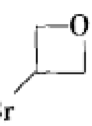
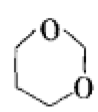
(d) $Cl—CH_2—O—CH_2CH_2CH_3$ (e)  (f) 

(g)  (h) 

3−39 Give IUPAC names for the following compounds.

(a) $CH_3—O—CH(CH_3)CH_2OH$ (b) $Ph—O—CH_2CH_3$ (c)

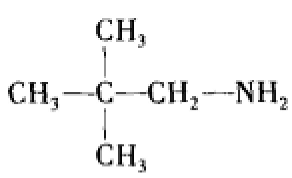
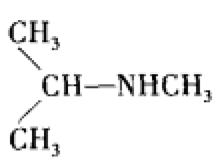
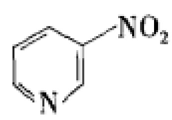
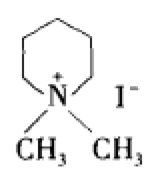
(d)  (e)  (f) 

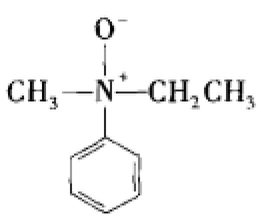
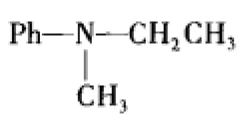
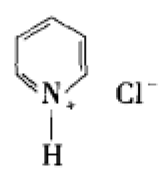
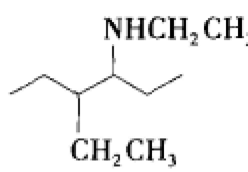
(g)  (h)  (i) 

3−40 For each compound,

(1) classify the nitrogen-containing functional groups.

(2) provide an acceptable name.

(a)  (b)  (c)  (d) 

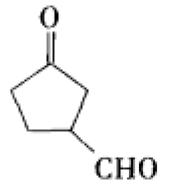
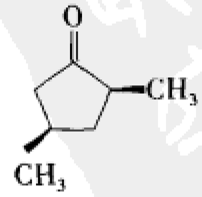
(e)  (f)  (g)  (h) 

3−41 Name the following ketones and aldehydes. When possible, give both a common name and an IUPAC name.

(a) $CH_3CO(CH_2)_4CH_3$ (b) $CH_3(CH_2)_2CO(CH_2)_2CH_3$ (c) $CH_3(CH_2)_5CHO$

(d) PhCOPh (e) $CH_3CH_2CH_2CHO$ (f) CH_3COCH_3

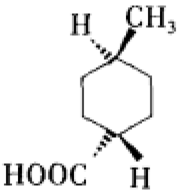
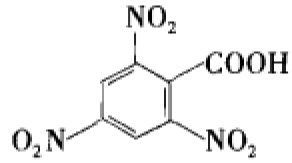
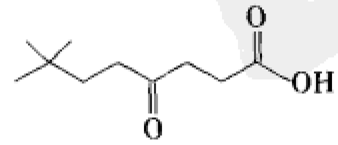
(g) $CH_3CH_2CHBrCH_2CH(CH_3)CHO$ (h) $Ph—CH{=}CH—CHO$ (i) $CH_3CH{=}CH—CH{=}CH—CHO$

(j) $CH_3CH_2COCH_2CHO$ (k)  (l) 

3−42 Give the IUPAC names of the following compounds.

(a) $PhCH_2CH_2COOH$ (b) $CH_3CH_2CH(CH_3)CO_2H$ (c) $CH_3CH(CH_3)CHBrCOOH$

(d) $HOOCCH_2CH(CH_3)CO_2H$ (e) $CH_3CH_2CH(CH_3)COONa$ (f) $(CH_3)_2C{=}CHCOOH$

(g)  (h)  (i) 

3−43 Draw the structures of the following compounds.

(**a**) ethanoic acid (**b**) phthalic acid (**c**) magnesium formate

(**d**) malonic acid (**e**) chloroacetic acid (**f**) acetyl chloride

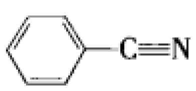
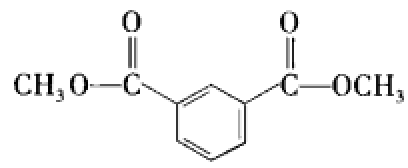
(**g**) zinc undecanoate (athlete's-foot powder) (**h**) sodium benzoate (a food preservative)

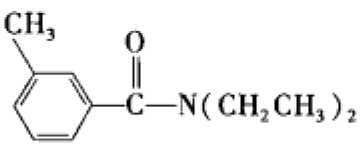
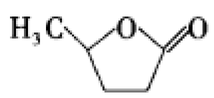
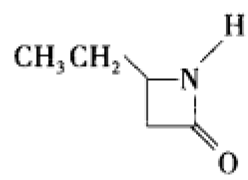
(**i**) sodium fluoroacetate (Compound 1080, a controversial coyote poison)

3−44 Give appropriate names for the following compounds:

(**a**) $CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2-\overset{O}{\overset{\|}{C}}-Cl$ (**b**) $Ph-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-H$ (**c**) $CH_3-\overset{O}{\overset{\|}{C}}-NH-Ph$

(**d**) $CH_3-NH-\overset{O}{\overset{\|}{C}}-Ph$ (**e**) $Ph-O-\overset{O}{\overset{\|}{C}}-CH_3$ (**f**) $Ph-\overset{O}{\overset{\|}{C}}-O-CH_3$

(**g**) 
(**h**)
(**i**) 

(**j**) 
(**k**) 
(**l**) 

Chapter 4

Structure and Stereochemistry of Alkanes

Whenever possible, we will study organic chemistry using families of compounds to organize the material. The properties and reactions of the compounds in a family are similar, just as their structures are similar. By considering how the structural features of a class of compounds determine their properties, we can predict the properties and reactions of similar new compounds. This organization elevates organic chemistry from a catalog of many individual compounds to a systematic study of a few types of compounds. Families of organic molecules are classified according to their reactive parts, called *functional groups*.

An **alkane** is a hydrocarbon that contains only single bonds. The alkanes are the simplest and least reactive class of organic compounds because they contain only hydrogen and sp^3 hybridized carbon, and they have no reactive functional groups. Although alkanes undergo reactions such as cracking and combustion at high temperatures, they are much less reactive than other classes of compounds having functional groups.

4−1 Physical Properties of Alkanes

Alkanes are used primarily as fuels, solvents, and lubricants. Natural gas, gasoline, kerosene, heating oil, lubricating oil, and paraffin "wax" are all composed primarily of alkanes, with different physical properties resulting from different ranges of molecular weights.

4−1A Solubilities and Densities of Alkanes

Alkanes are nonpolar, so they dissolve in nonpolar or weakly polar organic solvents. Alkanes are said to be **hydrophobic** ("water hating") because they do not dissolve in water. Alkanes are good lubricants and preservatives for metals because they keep water from reaching the metal surface and causing corrosion.

Densities of the *n*-alkanes are listed in Table 4−1. Alkanes have densities around 0.7 g/mL, compared with a density of 1.0 g/mL for water. Because alkanes are less dense than water and insoluble in water, a mixture of an alkane (such as gasoline or oil) and water quickly separates into two phases, with the alkane on top.

TABLE 4−1 Formulas and Physical Properties of the Unbranched Alkanes, Called the *n*-Alkanes

Alkane	Formula	Boiling Point/℃	Melting Point/℃	Density[a]/(g · mL^{-1})
methane	CH_4	−164	−183	0.55
ethane	C_2H_6	−89	−183	0.51
propane	C_3H_8	−42	−189	0.50

Continue

Alkane	Formula	Boiling Point/℃	Melting Point/℃	Density[a]/(g · mL⁻¹)
butane	C_4H_{10}	0	-138	0.58
pentane	C_5H_{12}	36	-130	0.63
hexane	C_6H_{14}	69	-95	0.66
heptane	C_7H_{16}	98	-91	0.68
octane	C_8H_{18}	126	-57	0.70
nonane	C_9H_{20}	151	-51	0.72
decane	$C_{10}H_{22}$	174	-30	0.73
undecane	$C_{11}H_{24}$	196	-26	0.74
dodecane	$C_{12}H_{26}$	216	-10	0.75
tridecane	$C_{13}H_{28}$	235	-5	0.76
tetradecane	$C_{14}H_{30}$	254	6	0.76
pentadecane	$C_{15}H_{32}$	271	10	0.77
hexadecane	$C_{16}H_{34}$	287	18	0.77
heptadecane	$C_{17}H_{36}$	303	23	0.76
octadecane	$C_{18}H_{38}$	317	28	0.76
nonadecane	$C_{19}H_{40}$	330	32	0.78
eicosane	$C_{20}H_{42}$	343	37	0.79
triacontane	$C_{30}H_{62}$	>450	66	0.81

[a]Densities are given at 20 ℃, except for methane and ethane, whose densities are given at their boiling points.

4-1B Boiling Points of Alkanes

Table 4-1 also gives the boiling points and melting points of the unbranched alkanes. The boiling points increase smoothly with increasing numbers of carbon atoms and increasing molecular weights. Larger molecules have larger surface areas, resulting in increased intermolecular van der Waals attractions. These increased attractions must be overcome for vaporization and boiling to occur. Thus, a larger molecule, with greater surface area and greater van der Waals attractions, boils at a higher temperature.

A graph of *n*-alkane boiling points versus the number of carbon atoms (Figure 4-1) shows the increase in boiling points with increasing molecular weight. Each additional CH_2 group increases the boiling point by about 30 ℃ up to about ten carbons, and by about 20 ℃ in higher alkanes.

Figure 4-1 also represents the boiling points of some branched alkanes. In general, a branched alkane boils at a lower temperature than the *n*-alkane with the same number of carbon atoms. This difference in boiling

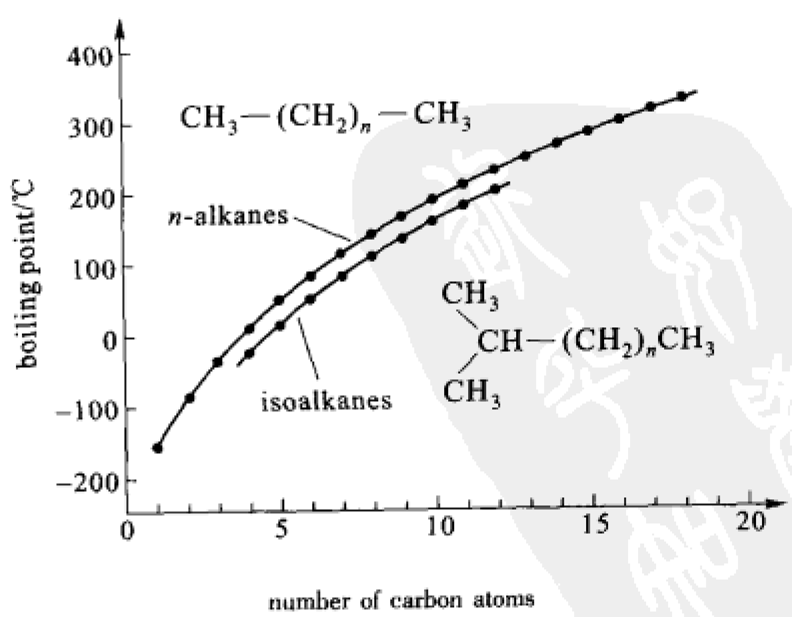


Figure 4-1 Alkane boiling points. The boiling points of the unbranched alkanes are compared with those of some branched alkanes. Because of their smaller surface areas, branched alkanes have lower boiling points than unbranched alkanes.

points arises because branched alkanes are more compact, with less surface area for London force interactions.

4-1C Melting Points of Alkanes

Figure 4-2 is a graph of the melting points of the n-alkanes. Like their boiling points, the melting points increase with increasing molecular weight. The melting point graph is not smooth, however. Alkanes with even numbers of carbon atoms pack better into a solid structure, so that higher temperatures are needed to melt them. Alkanes with odd numbers of carbon atoms do not pack as well, and they melt at lower temperatures. The saw-tooth-shaped graph of melting points is smoothed by drawing separate lines for the alkanes with even and odd numbers of carbon atoms.

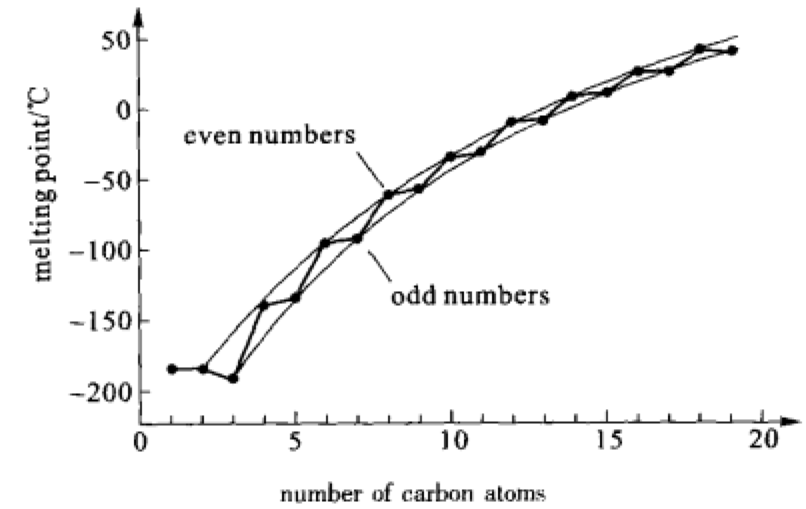
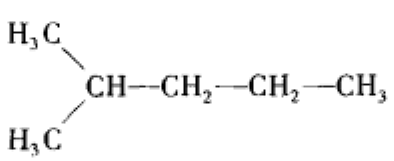
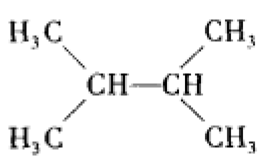


Figure 4-2 Alkane melting points. The melting point curve for n-alkanes with even numbers of carbon atoms is slightly higher than the curve for alkanes with odd numbers of carbons.

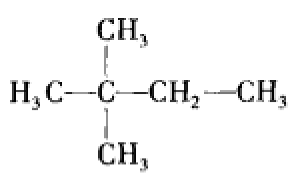
Branching of the chain also affects an alkane's melting point. A branched alkane generally melts at a *higher* temperature than the n-alkane with the same number of carbon atoms. Branching of an alkane gives it a more compact three-dimensional structure, which packs more easily into a solid structure and increases the melting point. The boiling points and melting points of three isomers of formula C_6H_{14} show that the boiling points decrease and the melting points increase as the shape of the molecule becomes more highly branched and compact.



bp 60 ℃
mp -154 ℃



bp 58 ℃
mp -135 ℃



bp 50 ℃
mp -98 ℃

PROBLEM 4-1

List each set of compounds in order of increasing boiling point and increasing melting point.

(a) hexane, octane, and decane

(b) octane, $(CH_3)_3C-C(CH_3)_3$, and $CH_3CH_2C(CH_3)_2CH_2CH_2CH_3$

4-2 Uses and Sources of Alkanes

Distillation separates alkanes into fractions with similar boiling points. These fractions are suited for different uses based on their physical properties, such as volatility and viscosity.

4-2A Major Uses of Alkanes

C_1—C_2 The first four alkanes (methane, ethane, propane, and butane) are gases at room temperature and at-

mospheric pressure. Methane and ethane are difficult to liquefy, so they are usually handled as compressed gases. Upon cooling to cryogenic (very low) temperatures, however, methane and ethane become liquids. *Liquefied natural gas*, mostly methane, can be transported in special refrigerated tankers more easily than it can be transported as a compressed gas.

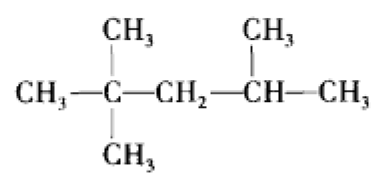
C_3—C_4 Propane and butane are easily liquefied at room temperature under modest pressure. These gases, often obtained along with liquid petroleum, are stored in low-pressure cylinders of *liquefied petroleum gas* (*LPG*). Propane and butane are good fuels, both for heating and for internal combustion engines. They burn cleanly, and pollution-control equipment is rarely necessary. In many agricultural areas, propane and butane are more cost-effective tractor fuels than gasoline and diesel fuel. Propane and butane have largely replaced Freons® (see Section 7-2D) as propellants in aerosol cans. Unlike alkanes, the chlorofluorocarbon Freon propellants are suspected of damaging the earth's protective ozone layer.

C_5—C_8 The next four alkanes are free-flowing, volatile liquids. Isomers of pentane, hexane, heptane, and octane are the primary constituents of gasoline. Their volatility is crucial for this use because the injection system simply squirts a stream of gasoline into the intake air as it rushes through. If gasoline did not evaporate easily, it would reach the cylinder in the form of droplets. Droplets cannot burn as efficiently as a vapor, so the engine would smoke and give low mileage.

In addition to being volatile, gasoline must resist the potentially damaging explosive combustion known as *knocking*. The antiknock properties of gasoline are rated by an **octane number** that is assigned by comparing the gasoline to a mixture of *n*-heptane (which knocks badly) and isooctane (2,2,4-trimethylpentane, which is not prone to knocking). The gasoline being tested is used in a test engine with variable compression ratio. Higher compression ratios induce knocking, so the compression ratio is increased until knocking begins. Tables are available that show the percentage of isooctane in an isooctane/heptane blend that begins to knock at any given compression ratio. The octane number assigned to the gasoline is simply the percentage of isooctane in an isooctane/heptane mixture that begins to knock at that same compression ratio.

$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$

n-heptane (0 octane)
(正庚烷)
prone to knocking



2,2,4-trimethylpentane (100 octane)
(2,2,4-三甲基戊烷)
"isooctane," resists knocking

C_9—C_{16} The nonanes (C_9) through about the hexadecanes (C_{16}) are higher-boiling liquids that are somewhat viscous. These alkanes are used in kerosene, jet fuel, and diesel fuel. **Kerosene**, the lowest-boiling of these fuels, was once widely available but is now harder to find. It is less volatile than gasoline and less prone to forming explosive mixtures. Kerosene was used in kerosene lamps and heaters, which use wicks to allow this heavier fuel to burn. Jet fuel is similar to kerosene, but more highly refined and less odorous.

Diesel fuel is not very volatile, so it does not evaporate in the intake air. In a diesel engine, the fuel is sprayed directly into the cylinder right at the top of the compression stroke. The hot, highly compressed air in the cylinder causes the fuel to burn quickly, swirling and vaporizing as it burns. Some of the alkanes in diesel fuel have fairly high freezing points, and they may solidify in cold weather. This partial solidification causes the diesel fuel to turn into a waxy, semisolid mass. Owners of diesel engines in cold climates often mix a small amount of gasoline with their diesel fuel in the winter. The added gasoline dissolves the frozen alkanes, diluting the slush and allowing it to be pumped to the cylinders.

C_{16} and Up Alkanes with more than 16 carbon atoms are most often used as lubricating and heating oils. These

are sometimes called "mineral" oils because they come from petroleum, which was once considered a mineral.

Paraffin "wax" is not a true wax, but a purified mixture of high-molecular-weight alkanes with melting points well above room temperature. The true waxes are long-chain esters, discussed in Chapter 26.

4-2B Alkane Sources; Petroleum Refining

Alkanes are derived mostly from petroleum and petroleum by-products. *Petroleum*, often called *crude oil*, is pumped from wells that reach into pockets containing the remains of prehistoric plants. The principal constituents of crude oil are alkanes, some aromatics, and some undesirable compounds containing sulfur and nitrogen. The composition of petroleum and the amounts of contaminants vary from one source to another, and a refinery must be carefully adjusted to process a particular type of crude oil. Because of their different qualities, different prices are paid for light Arabian crude, West Texas crude, and other classes of crude petroleum.

The first step in refining petroleum is a careful fractional distillation. The products of that distillation are not pure alkanes but mixtures of alkanes with useful ranges of boiling points. Table 4-2 shows the major fractions obtained from distillation of crude petroleum.

TABLE 4-2 Major Fractions Obtained from Distillation of Crude Petroleum

Boiling Range/℃	Number of Carbons	Fraction	Use
under 30°	2-4	petroleum gas	LP gas for heating
30°-180°	4-9	gasoline	motor fuel
160°-230°	8-16	kerosene	heat, jet fuel
200°-320°	10-18	diesel	motor fuel
300°-450°	16-30	heavy oil	heating, lubrication
>300° (vacuum)	>25	petroleum "jelly" paraffin "wax"	
residue	>35	asphalt	

After distillation, **catalytic cracking** converts some of the less valuable fractions to more valuable products. Catalytic cracking involves heating alkanes in the presence of materials that catalyze the cleavage of large molecules into smaller ones. Cracking is often used to convert higher-boiling fractions into mixtures that can be blended with gasoline. When cracking is done in the presence of hydrogen (**hydrocracking**), the product is a mixture of alkanes free of sulfur and nitrogen impurities. The following reaction shows the catalytic hydrocracking of a molecule of tetradecane into two molecules of heptane.

$$CH_3-(CH_2)_{12}-CH_3 + H_2 \xrightarrow[SiO_2 \text{ or } Al_2O_3 \text{ catalyst}]{\text{heat}} 2CH_3-(CH_2)_5-CH_3$$

4-2C Natural Gas; Methane

Natural gas was once treated as a waste product of petroleum production and destroyed by flaring it off. Now natural gas is an equally valuable natural resource, pumped and stored throughout the world. Natural gas is about 70% methane, 10% ethane, and 15% propane, depending on the source of the gas. Small amounts of other hydrocarbons and contaminants are also present. Natural gas is often found above pockets of petroleum or coal, although it is also found in places where there is little or no recoverable petroleum or coal. Natural gas is used primarily as a fuel to heat buildings and to generate electricity. It is also important as a starting material for the production of fertilizers.

Although the methane we burn as natural gas is millions of years old, another 300 million tons per year

(estimated) of new methane is synthesized by microbes in diverse places such as the stomachs of plant-eating animals and the mud under the seafloor. Most of the undersea methane is eaten by other microbes, but some escapes at methane seeps. Under the sea, cold, high-pressure conditions may allow formation of **methane hydrate**, with individual methane molecules trapped inside cages of water molecules. When methane hydrate is brought to the surface, it quickly melts and the methane escapes. We currently have no practical methods for capturing and using microbial methane or methane hydrate. Much of this methane escapes to the atmosphere, where it acts as a greenhouse gas and contributes to global warming.

4-3 Reactions of Alkanes

Alkanes are the least reactive class of organic compounds. Their low reactivity is reflected in another term for alkanes: **paraffins.** The name *paraffin* comes from two Latin terms, *parum*, meaning "too little," and *affinis*, meaning "affinity." Chemists found that alkanes do not react with strong acids or bases or with most other reagents. They attributed this low reactivity to a lack of affinity for other reagents, so they coined the name "paraffins."

Most useful reactions of alkanes take place under energetic or high-temperature conditions. These conditions are inconvenient in a laboratory because they require specialized equipment, and the rate of the reaction is difficult to control. Alkane reactions often form mixtures of products that are difficult to separate. These mixtures may be of commercial importance for an industry, however, where the products may be separated and sold separately. Newer methods of selective functionalization may eventually change this picture. For now, however, the following alkane reactions are rarely seen in laboratory applications, but they are widely used in the chemical industry and even in your home and car.

4-3A Combustion

Combustion is a rapid oxidation that takes place at high temperatures, converting alkanes to carbon dioxide and water. Little control over the reaction is possible, except for moderating the temperature and controlling the fuel/air ratio to achieve efficient burning.

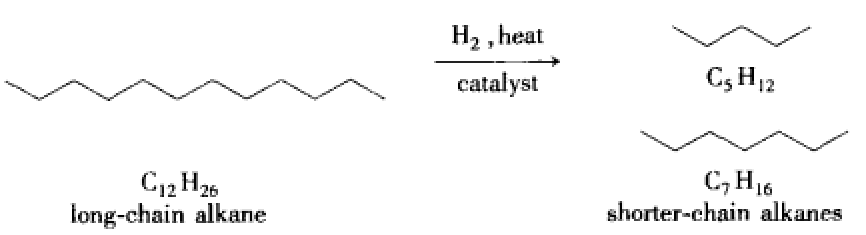
$$C_nH_{(2n+2)} + \text{excess } O_2 \xrightarrow{\text{heat}} n\,CO_2 + (n+1)H_2O$$

Unfortunately, the burning of gasoline and fuel oil pollutes the air and depletes the petroleum resources needed for lubricants and chemical feedstocks. Solar and nuclear heat sources cause less pollution, and they do not deplete these important natural resources. Facilities that use these more environment-friendly heat sources are, however, more expensive than those that rely on the combustion of alkanes.

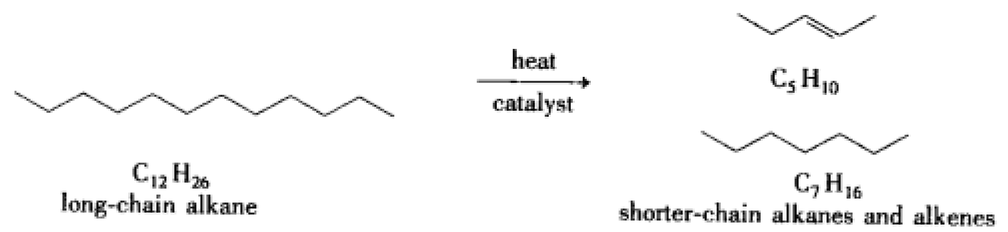
4-3B Cracking and Hydrocracking

As discussed in Section 4-2B, catalytic **cracking** of large hydrocarbons at high temperatures produces smaller hydrocarbons. The cracking process usually operates under conditions that give the maximum yields of gasoline. In **hydrocracking**, hydrogen is added to give saturated hydrocarbons; cracking without hydrogen gives mixtures of alkanes and alkenes.

Catalytic hydrocracking



Catalytic cracking



4-3C Halogenation

Alkanes can react with halogens (F_2, Cl_2, Br_2, I_2) to form alkyl halides. For example, methane reacts with chlorine (Cl_2) to form chloromethane (methyl chloride), dichloromethane (methylene chloride), trichloromethane (chloroform), and tetrachloromethane (carbon tetrachloride).

$$CH_4 + Cl_2 \xrightarrow{\text{heat or light}} CH_3Cl + CH_2Cl_2 + CHCl_3 + CCl_4 + HCl$$

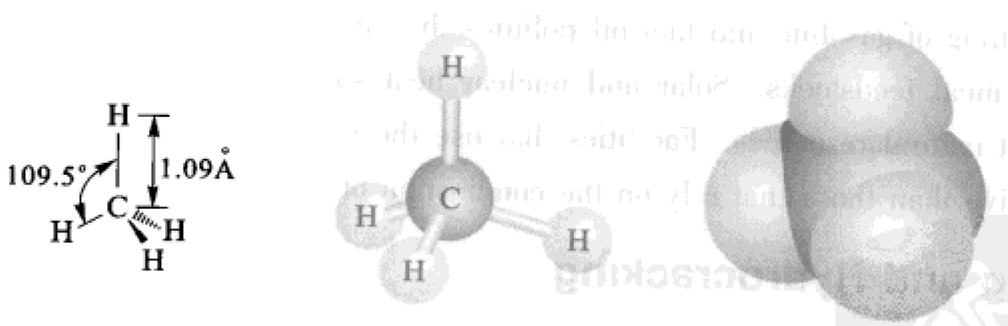
Heat or light is usually needed to initiate this **halogenation**. Reactions of alkanes with chlorine and bromine proceed at moderate rates and are easily controlled. Reactions with fluorine are often too fast to control, however. Iodine reacts very slowly or not at all. We will discuss the halogenation of alkanes in Chapter 5.

4-4 Structure and Conformations of Alkanes

Although alkanes are not as reactive as other classes of organic compounds, they have many of the same structural characteristics. We will use simple alkanes as examples to study some of the properties of organic compounds, including the structure of sp^3 hybridized carbon atoms and properties of C—C and C—H single bonds.

4-4A Structure of Methane

The simplest alkane is *methane*, CH_4. Methane is perfectly tetrahedral, with the 109.5° bond angles predicted for an sp^3 hybrid carbon. Four hydrogen atoms are covalently bonded to the central carbon atom, with bond lengths of 1.09 Å.

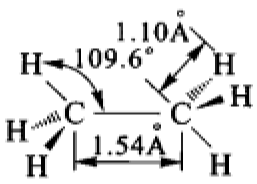


4-4B Conformations of Ethane

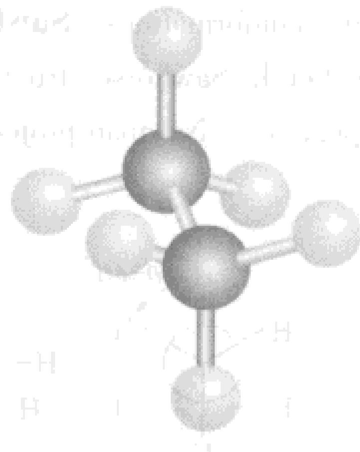
Ethane, the two-carbon alkane, is composed of two methyl groups with overlapping sp^3 hybrid orbitals forming a sigma bond between them.

The two methyl groups are not fixed in a single position but are relatively free to rotate about the sigma bond connecting the two carbon atoms. The bond maintains its linear bonding overlap as the carbon atoms turn. The different arrangements formed by rotations about a single bond are called **conformations**, and a specific conformation is called a **conformer** ("**confor**mational iso**mer**"). Pure conformers cannot be isolated in most cases,

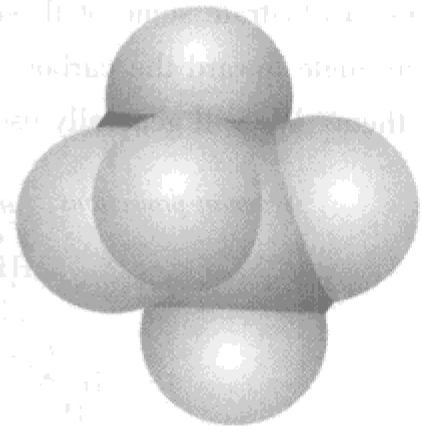
because the molecules are constantly rotating through all the possible conformations.



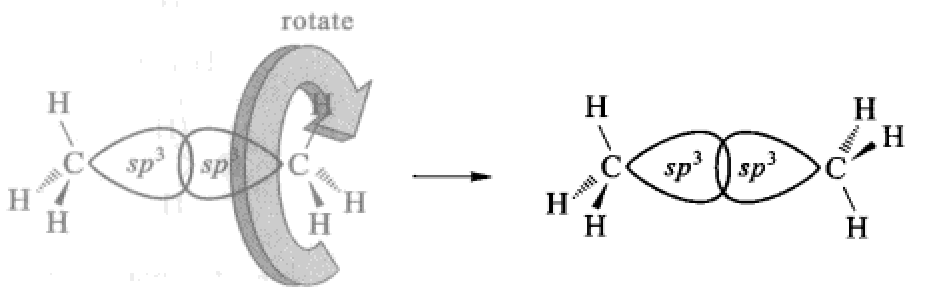
ethane



ethane

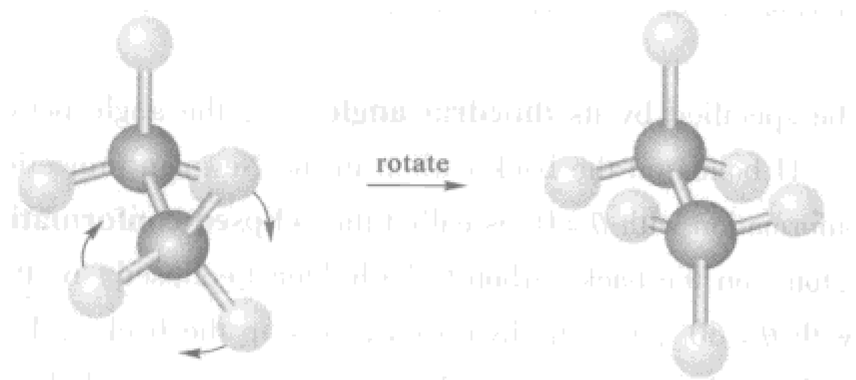


ethane

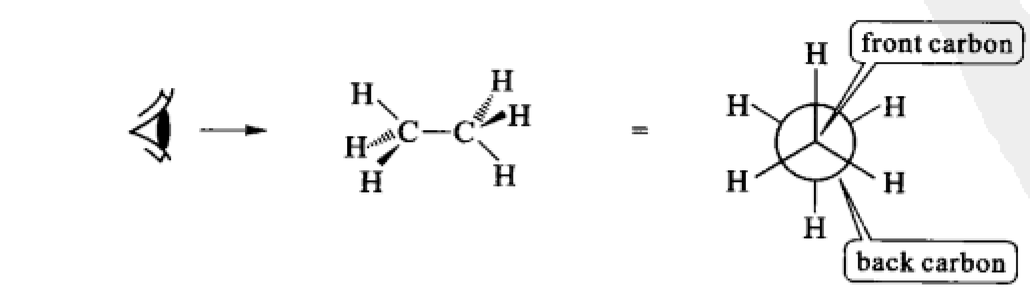


linear overlap of sigma bond

overlap maintained



In drawing conformations, we often use **Newman projections**, a way of drawing a molecule looking straight down the bond connecting two carbon atoms (Figure 4-3). The front carbon atom is represented by three lines (three bonds) coming together in a Y shape. The back carbon is represented by a circle with three bonds pointing out from it. Until you become familiar with Newman projections, you should make models and compare your models with the drawings.



viewed from the end

perspective drawing

Newman projection
(纽曼投影式)

Figure 4-3 The Newman projection looks straight down the carbon-carbon bond.

An infinite number of conformations are possible for ethane, because the angle between the hydrogen atoms on the front and back carbons can take on an infinite number of values. Figure 4–4 uses Newman projections and sawhorse structures to illustrate some of these ethane conformations. **Sawhorse structures** picture the molecule looking down at an angle toward the carbon-carbon bond. Sawhorse structures can be misleading, depending on how the eye sees them. We will generally use perspective or Newman projections to draw molecular conformations.

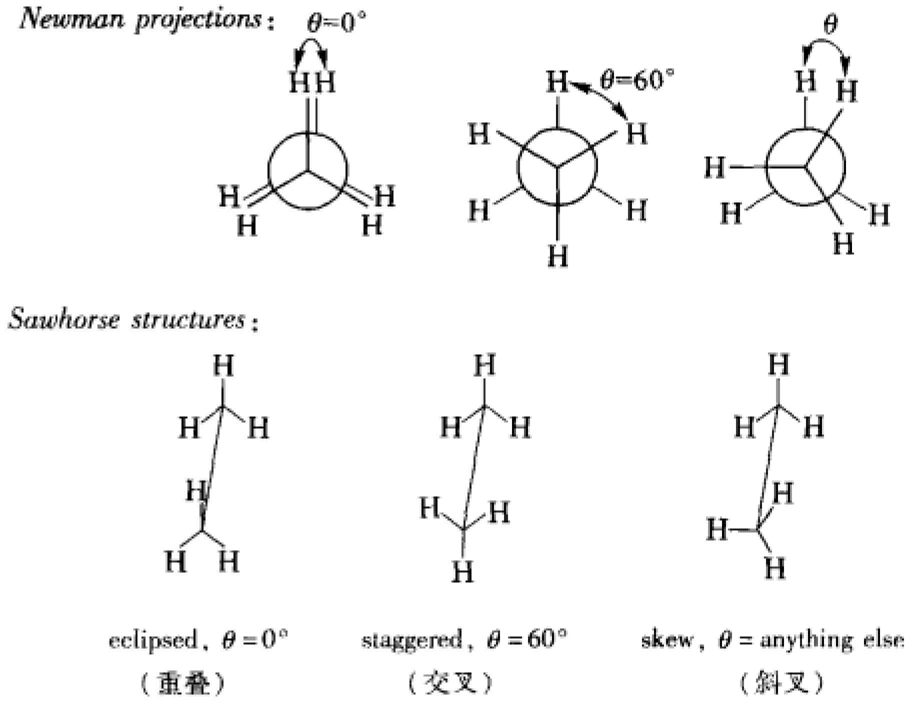


Figure 4–4 Ethane conformations. The eclipsed conformation has a dihedral angle $\theta = 0°$, and the staggered conformation has $\theta = 60°$. Any other conformation is called a *skew* conformation.

Any conformation can be specified by its **dihedral angle** (θ), the angle between the C—H bonds on the front carbon atom and the C—H bonds on the back carbon in the Newman projection. Two of the conformations have special names. The conformation with $\theta = 0°$ is called the **eclipsed conformation** because the Newman projection shows the hydrogen atoms on the back carbon to be hidden (eclipsed) by those on the front carbon. The **staggered conformation**, with $\theta = 60°$, has the hydrogen atoms on the back carbon staggered halfway between the hydrogens on the front carbon. Any other intermediate conformation is called a **skew conformation**.

In a sample of ethane gas at room temperature, the ethane molecules are rotating and their conformations are constantly changing. These conformations are not all equally favored, however. The lowest-energy conformation is the staggered conformation, with the electron clouds in the C—H bonds separated as much as possible. The eclipsed conformation places the C—H electron clouds closer together; it is about 12.6 kJ/mol higher in energy than the staggered conformation. Three kilocalories is not a large amount of energy, and at room temperature, most molecules have enough kinetic energy to overcome this small rotational barrier.

Figure 4–5 shows how the potential energy of ethane changes as the carbon-carbon bond rotates. The y axis shows the potential energy relative to the most stable (staggered) conformation. The x axis shows the dihedral angle as it increases from 0° (eclipsed) through 60° (staggered) and on through additional eclipsed and staggered conformations as θ continues to increase. As ethane rotates toward an eclipsed conformation, its potential energy increases, and there is resistance to the rotation. This resistance to twisting (torsion) is called **torsional strain**, and the 12.6 kJ/mol of energy required is called **torsional energy**.

Conformational analysis is the study of the energetics of different conformations. Many reactions depend on a molecule's ability to twist into a particular conformation; conformational analysis can help to predict which conformations are favored and which reactions are more likely to take place. We will apply conformational analysis

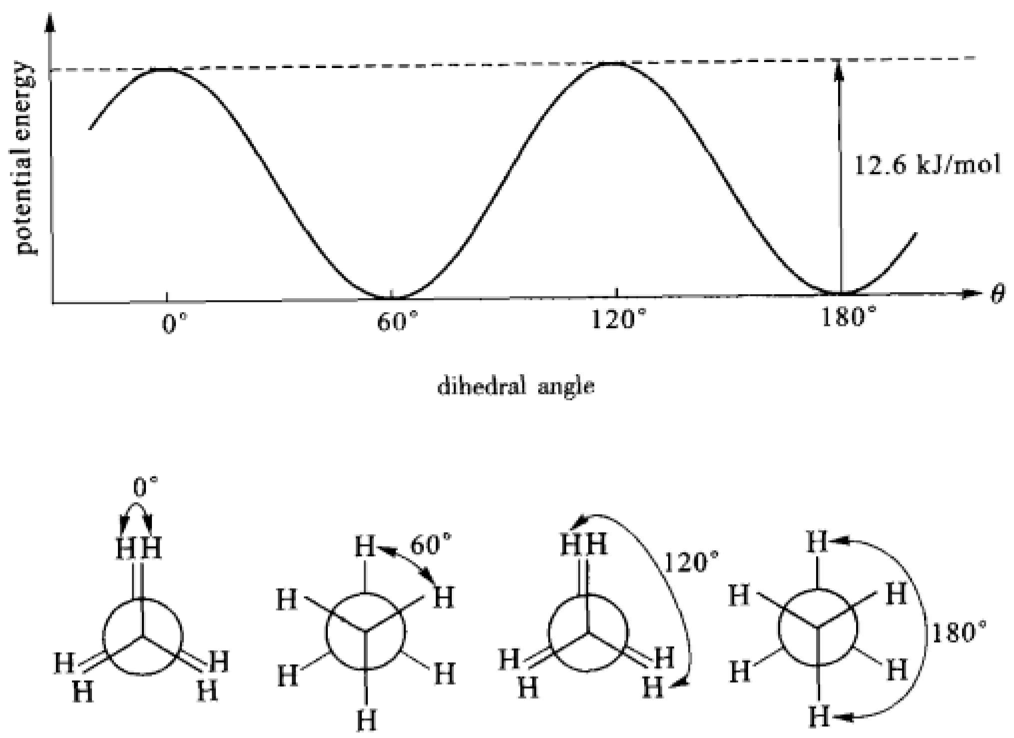


Figure 4−5 The torsional energy of ethane is lowest in the staggered conformation. The eclipsed conformation is about 12.6 kJ/mol higher in energy. At room temperature, this barrier is easily overcome and the molecules rotate constantly.

to propane and butane first, and later to some interesting cycloalkanes.

4−4C Conformations of Butane

Butane is the four-carbon alkane, with molecular formula C_4H_{10}. We refer to *n*-butane as a straight-chain alkane, but the chain of carbon atoms is not really straight. The angles between the carbon atoms are close to the tetrahedral angle, about 109.5°. Rotations about any of the carbon-carbon bonds are possible; Figure 4−6 shows Newman projections, looking along the central C2—C3 bond, for four conformations of butane. Construct butane with your molecular models, and sight down the C2—C3 bond. Notice that we have defined the dihedral angle θ as the angle between the two end methyl groups.

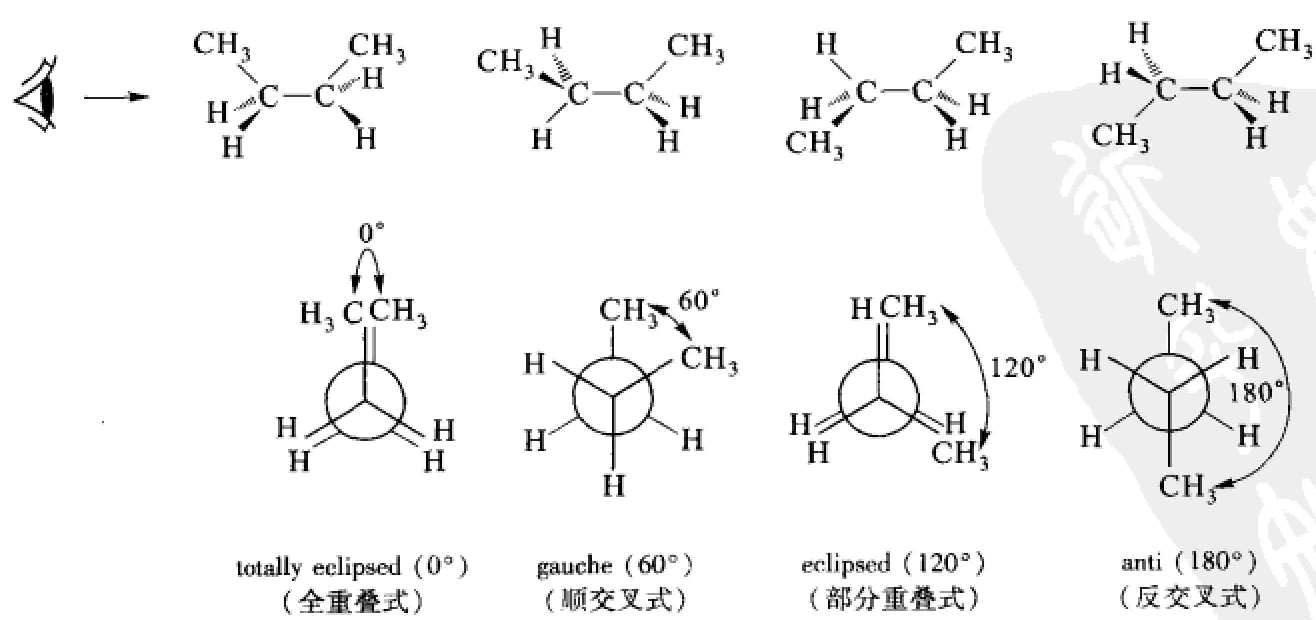


Figure 4−6 Butane conformations. Rotations about the center bond in butane give different molecular shapes. Three of these conformations have specific names.

Three of the conformations shown in Figure 4−6 are given special names. When the methyl groups are

pointed in the same direction ($\theta = 0°$), they eclipse each other. This conformation is called **totally eclipsed**, to distinguish it from the other eclipsed conformations like the one at $\theta = 120°$. At $\theta = 60°$, the butane molecule is staggered and the methyl groups are toward the left and right of each other. This 60° conformation is called **gauche** (pronounced gōsh), a French word meaning "left" or "awkward."

Another staggered conformation occurs at $\theta = 180°$, with the methyl groups pointing in opposite directions. This conformation is called **anti** because the methyl groups are "opposed."

Torsional Energy of Butane A graph of the relative torsional energies of the butane conformations is shown in Figure 4-7. All the staggered conformations (anti and gauche) are lower in energy than any of the eclipsed conformations. The anti conformation is lowest in energy because it places the bulky methyl groups as far apart as possible. The gauche conformations, with the methyl groups separated by just 60°, are 3.8 kJ higher in energy than the anti conformation because the methyl groups are close enough that their electron clouds begin to repel each other. Use your molecular models to compare the crowding of the methyl groups in these conformations.

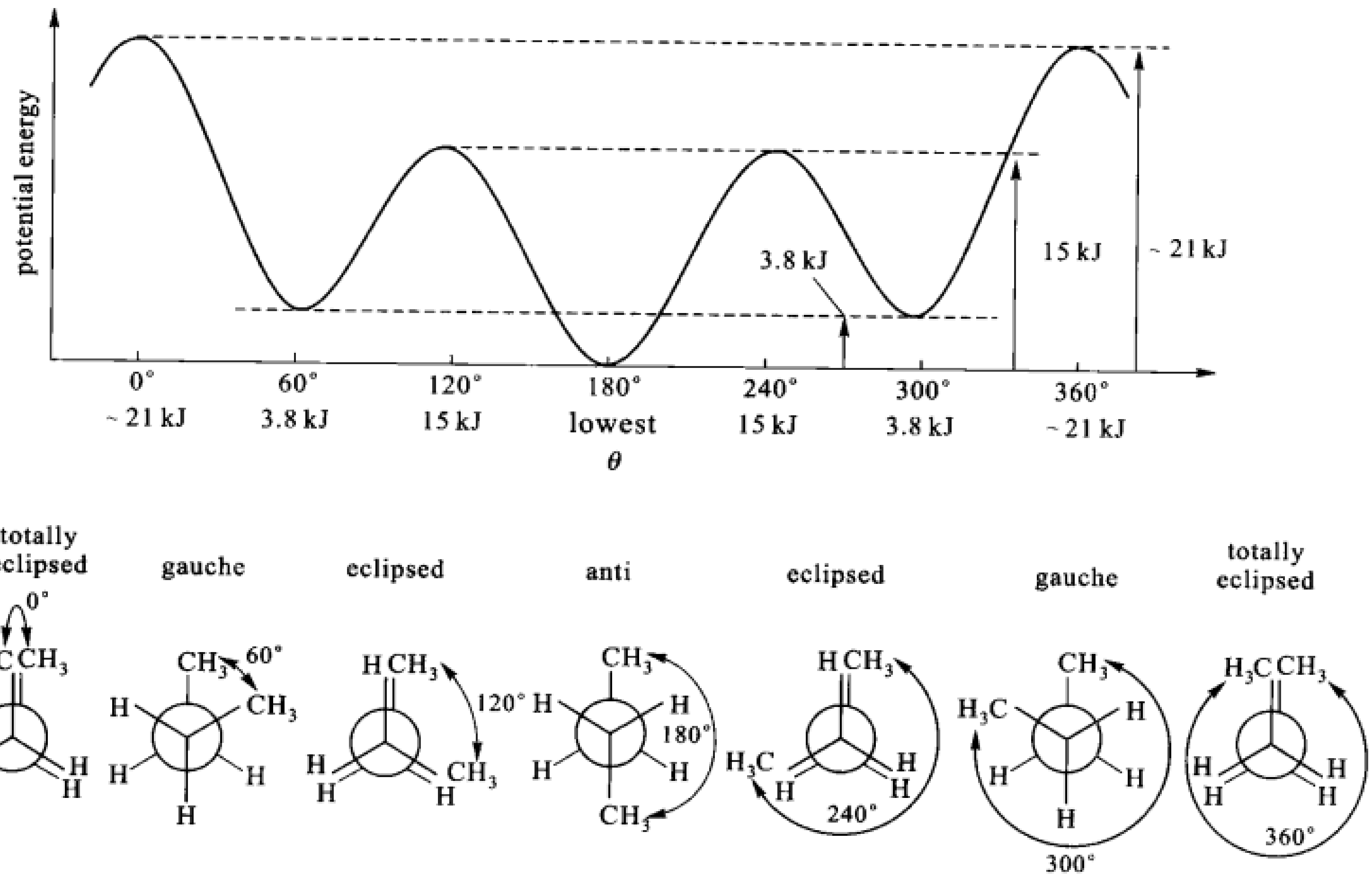
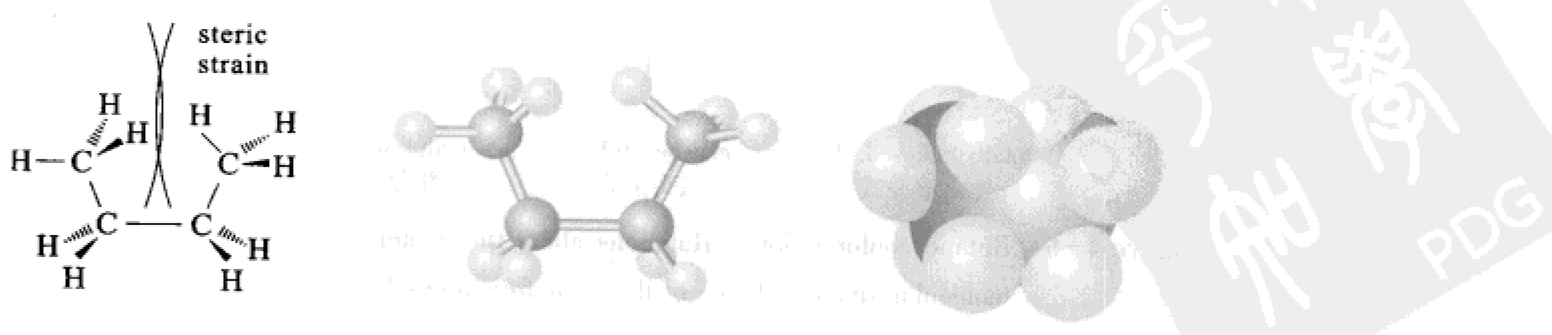


Figure 4-7 Torsional energy of butane. The anti conformation is lowest in energy, and the totally eclipsed conformation is highest in energy.

Steric Strain The totally eclipsed conformation is about 6 kJ higher in energy than the other eclipsed conformations because it forces the two end methyl groups so close together that their electron clouds experience a strong repulsion. This kind of interference between two bulky groups is called **steric strain** or **steric hindrance**. The following structure shows the interference between the methyl groups in the totally eclipsed conformation.



Totally eclipsed conformation of butane

Rotating the totally eclipsed conformation 60° to a gauche conformation releases most, but not all, of this steric strain. The gauche conformation is still 3.8 kJ higher in energy than the most stable anti conformation.

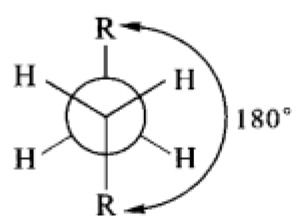
What we have learned about the conformations of butane can be applied to other alkanes. We can predict that carbon-carbon single bonds will assume staggered conformations whenever possible to avoid eclipsing of the groups attached to them. Among the staggered conformations, the anti conformation is preferred because it has the lowest torsional energy. We must remember, however, that there is enough thermal energy present at room temperature for the molecules to rotate rapidly among all the different conformations. The relative stabilities are important because more molecules will be found in the more stable conformations than in the less stable ones.

PROBLEM 4-2

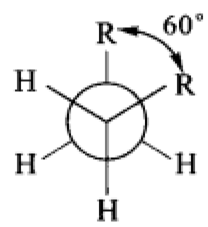
Draw a graph, similar to Figure 4-7, of the torsional energy of 2-methylbutane as it rotates about the C2—C3 bond.

4-4D Conformations of Higher Alkanes

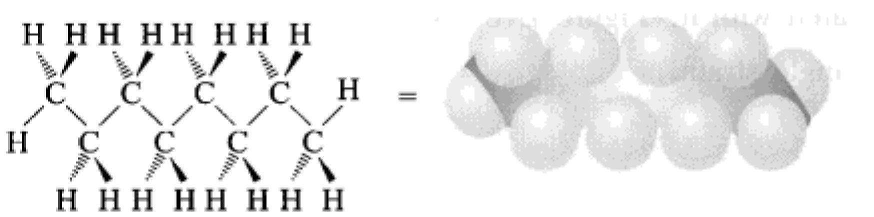
The higher alkanes resemble butane in their preference for anti and gauche conformations about the carbon-carbon bonds. The lowest-energy conformation for any straight-chain alkane is the one with all the internal carbon-carbon bonds in its anti conformations. These anti conformations give the chain a zigzag shape. At room temperature, the internal carbon-carbon bonds undergo rotation, and many molecules contain gauche conformations. Gauche conformations make kinks in the zigzag structure. Nevertheless, we frequently draw alkane chains in a zigzag structure to represent the most stable arrangement.



anti conformation
（反交叉式构象）



gauche conformation
（顺交叉式构象）



octane, all anti conformation
（辛烷，全部反交叉式）

4-5 Cycloalkanes

Many organic compounds are **cyclic**: They contain rings of atoms. The carbohydrates we eat are cyclic, the nucleotides that make up our DNA and RNA are cyclic, and the antibiotics we use to treat diseases are cyclic. In this chapter, we use the *cycloalkanes* to illustrate the properties and stability of cyclic compounds.

4-5A Physical Properties of Cycloalkanes

Most cycloalkanes resemble the **acyclic** (noncyclic), open-chain alkanes in their physical properties and in their chemistry. They are nonpolar, relatively inert compounds with boiling points and melting points that depend on their molecular weights. The cycloalkanes are held in a more compact cyclic shape, so their physical properties are similar to those of the compact, branched alkanes. The physical properties of some common cycloalkanes are listed in Table 4-3.

TABLE 4-3 Physical Properties of Some Simple Cycloalkanes

Cycloalkane	Formula	Boiling Point/℃	Melting Point/℃	Density/(g·mL^{-1})
cyclopropane(环丙烷)	C_3H_6	-33	-128	0.72
cyclobutane(环丁烷)	C_4H_8	-12	-50	0.75
cyclopentane(环戊烷)	C_5H_{10}	49	-94	0.75
cyclohexane(环己烷)	C_6H_{12}	81	7	0.78
cycloheptane(环庚烷)	C_7H_{14}	118	-12	0.81
cyclooctane(环辛烷)	C_8H_{16}	148	14	0.83

4-5B Stabilities of Cycloalkanes; Ring Strain

Although all the simple cycloalkanes (up to about C_{20}) have been synthesized, the most common rings contain five or six carbon atoms. We will study the stabilities and conformations of these rings in detail because they help to determine the properties of many important organic compounds.

Why are five-membered and six-membered rings more common than the other sizes? Adolf von Baeyer first attempted to explain the relative stabilities of cyclic molecules in the late nineteenth century, and he was awarded a Nobel Prize for this work in 1905. Baeyer reasoned that the carbon atoms in acyclic alkanes have bond angles of 109.5°. (We now explain this bond angle by the tetrahedral geometry of the sp^3 hybridized carbon atoms.)

If a cycloalkane requires bond angles other than 109.5°, the orbitals of its carbon-carbon bonds cannot achieve optimum overlap, and the cycloalkane must have some **angle strain** (sometimes called **Baeyer strain**) associated with it. Figure 4-8 shows that a planar cyclobutane, with 90° bond angles, is expected to have significant angle strain.

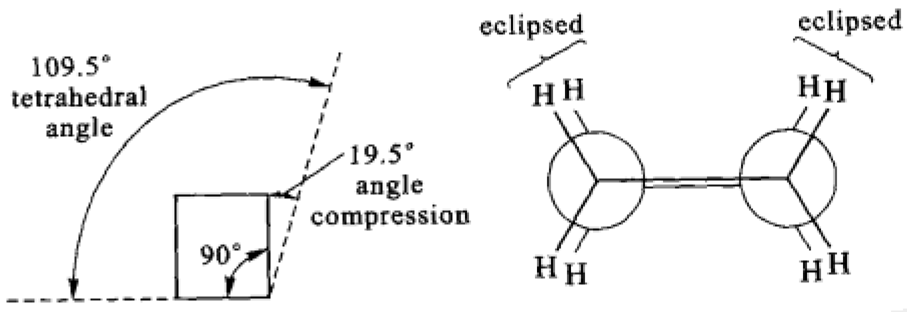


Figure 4-8 The ring strain of a planar cyclobutane results from two factors: angle strain from the compressing of the bond angles to 90° rather than the tetrahedral angle of 109.5°, and torsional strain from eclipsing of the bonds.

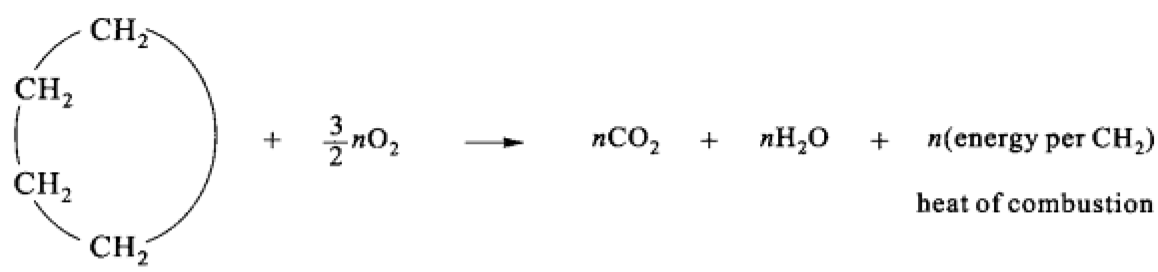
In addition to this angle strain, the Newman projection in Figure 4-8 shows that the bonds are eclipsed, resembling the *totally eclipsed* conformation of butane. This eclipsing of bonds gives rise to torsional strain. Together, the angle strain and the torsional strain add to give what we call the **ring strain** of the cyclic compound. The amount of ring strain depends primarily on the size of the ring.

Before we discuss the ring strain of different cycloalkanes, we need to consider how ring strain is measured. In theory, we should measure the total amount of energy in the cyclic compound and subtract the amount of energy

in a similar, strain-free reference compound. The difference should be the amount of extra energy due to ring strain in the cyclic compound. These measurements are commonly made using *heats of combustion*.

The **heat of combustion** is the amount of heat released when a compound is burned with an excess of oxygen in a sealed container called a *bomb calorimeter*. If the compound has extra energy as a result of ring strain, that extra energy is released in the combustion. The heat of combustion is usually measured by the temperature rise in the water bath surrounding the "bomb."

A cycloalkane can be represented by the molecular formula $(CH_2)_n$, so the general reaction in the bomb calorimeter is:



$$(CH_2)_n + \frac{3}{2}nO_2 \longrightarrow nCO_2 + nH_2O + n(\text{energy per } CH_2)$$

cycloalkane, $(CH_2)_n$
（环烷烃）

The molar heat of combustion of cyclohexane is nearly twice that of cyclopropane, simply because cyclohexane contains twice as many methylene (CH_2) groups per mole. To compare the relative stabilities of cycloalkanes, we divide the heat of combustion by the number of methylene (CH_2) groups. The result is the energy per CH_2 group. These normalized energies allow us to compare the relative amounts of ring strain (per methylene group) in the cycloalkanes.

Table 4-4 shows the heats of combustion for some simple cycloalkanes. The reference value of 658.6 kJ per mole of CH_2 groups comes from an unstrained long-chain alkane. The values show large amounts of ring strain in cyclopropane and cyclobutane. Cyclopentane, cycloheptane, and cyclooctane have much smaller amounts of ring strain, and cyclohexane has no ring strain at all. We will discuss several of these rings in detail to explain this pattern of ring strain.

TABLE 4-4 Heats of Combustion (per Mole) for Some Simple Cycloalkanes

Ring Size	Cycloalkane	Molar Heat of Combustion	Heat of Combustion per CH_2 Group	Ring Strain per CH_2 Group	Total Ring Strain
3	cyclopropane	2091 kJ	697.1 kJ	38.5 kJ	115 kJ
4	cyclobutane	2744 kJ	686.1 kJ	27.5 kJ	110 kJ
5	cyclopentane	3320 kJ	664.0 kJ	5.4 kJ	27 kJ
6	cyclohexane	3951 kJ	658.6 kJ	0.0 kJ	0.0 kJ
7	cycloheptane	4637 kJ	662.4 kJ	3.8 kJ	27 kJ
8	cyclooctane	5309 kJ	663.6 kJ	5.1 kJ	41 kJ
reference: long-chain alkane			658.6 kJ	0.0 kJ	0.0 kJ

4-5C Cyclopropane

Table 4-4 shows that cyclopropane bears more ring strain per methylene group than any other cycloalkane. Two factors contribute to this large ring strain. First is the angle strain required to compress the bond angles from the tetrahedral angle of 109.5° to the 60° angles of cyclopropane. The bonding overlap of the carbon-carbon sp^3 orbitals is weakened when the bond angles differ so much from the tetrahedral angle. The sp^3 orbitals cannot point

directly toward each other, and they overlap at an angle to form weaker "bent bonds" (Figure 4-9).

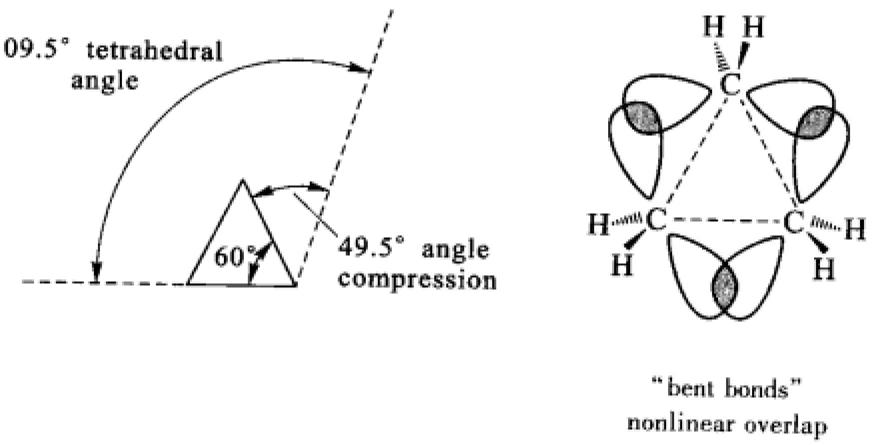


Figure 4-9 Angle strain in cyclopropane. The bond angles are compressed to 60° from the usual 109.5° bond angle of sp^3 hybridized carbon atoms. This severe angle strain leads to nonlinear overlap of the sp^3 orbitals and "bent bonds."

Torsional strain is the second factor in cyclopropane's large ring strain. The three-membered ring is planar, and all the bonds are eclipsed. A Newman projection of one of the carbon-carbon bonds (Figure 4-10) shows that the conformation resembles the totally eclipsed conformation of butane. The torsional strain in cyclopropane is not as great as its angle strain, but it helps to account for the large total ring strain.

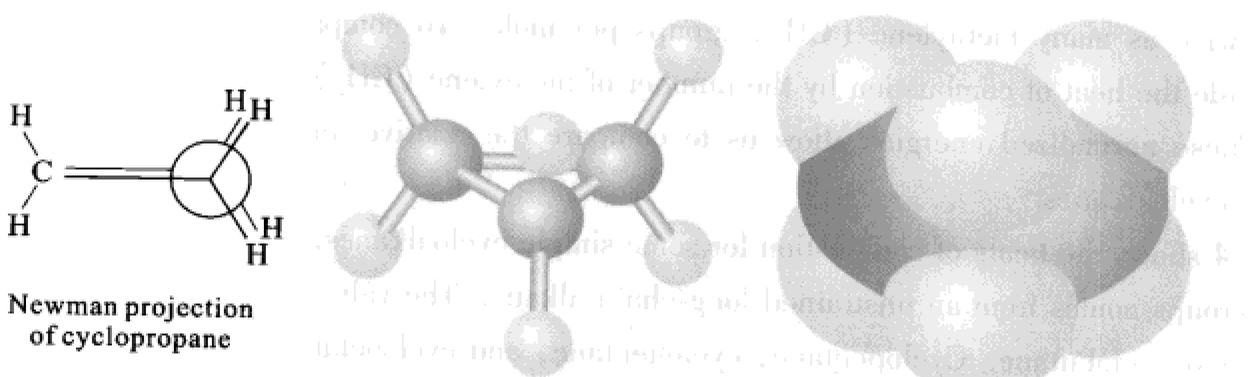


Figure 4-10 Torsional strain in cyclopropane. All the carbon-carbon bonds are eclipsed, generating torsional strain that contributes to the total ring strain.

Cyclopropane is generally more reactive than other alkanes. Reactions that open the cyclopropane ring release 115 kJ per mole of ring strain, which provides an additional driving force for these reactions.

4-5D Cyclobutane

The total ring strain in cyclobutane is almost as great as that in cyclopropane, but is distributed over four carbon atoms. If cyclobutane were perfectly planar and square, it would have 90° bond angles. A planar geometry requires eclipsing of all the bonds, however, as in cyclopropane. To reduce this torsional strain, cyclobutane actually assumes a slightly folded form, with bond angles of 88°. These smaller bond angles require slightly more angle strain than 90° angles, but the relief of some of the torsional strain appears to compensate for a small increase in angle strain (Figure 4-11).

PROBLEM 4-3

trans-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane, but *cis*-1,3-dimethylcyclobutane is more stable than *trans*-1,3-dimethylcyclobutane. Use drawings to explain these observations.

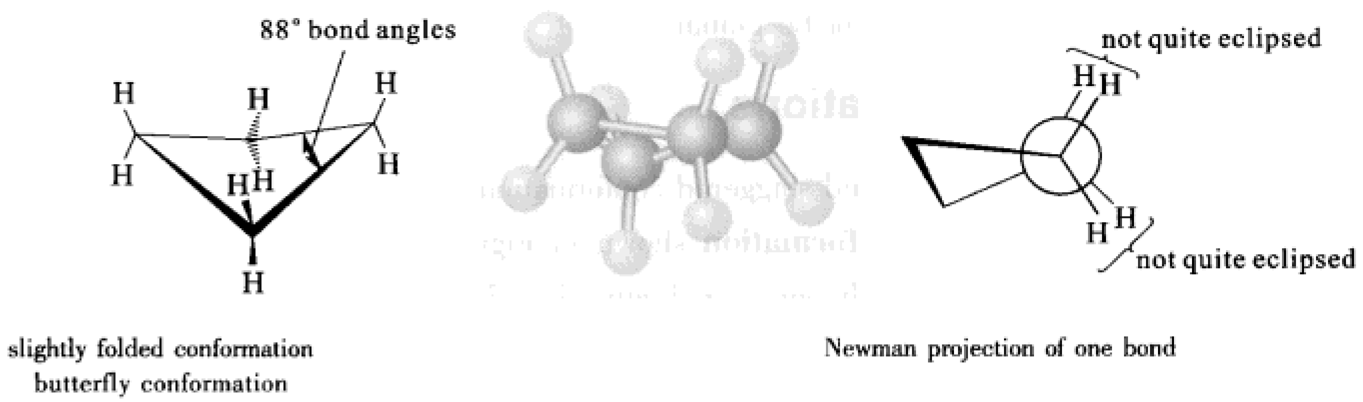


Figure 4−11 The conformation of cyclobutane is slightly folded. Folding gives partial relief from the eclipsing of bonds, as shown in the Newman projection. Compare this actual structure with the hypothetical planar structure in Figure 4−8.

4−5E Cyclopentane

If cyclopentane had the shape of a planar, regular pentagon, its bond angles would be 108°, close to the tetrahedral angle of 109.5°. A planar structure would require all the bonds to be eclipsed, however. Cyclopentane actually assumes a slightly puckered "envelope" conformation that reduces the eclipsing and lowers the torsional strain (Figure 4−12). This puckered shape is not fixed, but undulates by the thermal up-and-down motion of the five methylene groups. The "flap" of the envelope seems to move around the ring as the molecule undulates.

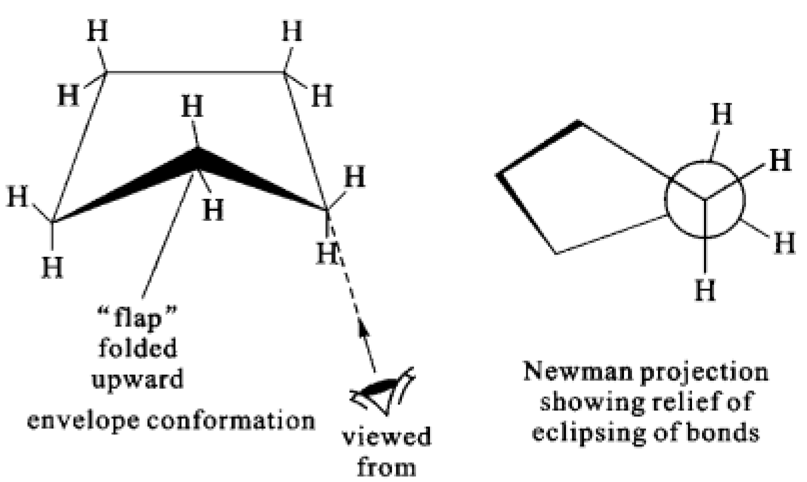


Figure 4−12 The conformation of cyclopentane is slightly folded, like the shape of an envelope. This puckered conformation reduces the eclipsing of adjacent CH_2 groups.

4−6 Cyclohexane Conformations

We will cover the conformations of cyclohexane in more detail than other cycloalkanes because cyclohexane ring systems are particularly common. Carbohydrates, steroids, plant products, pesticides, and many other important compounds contain cyclohexane-like rings whose conformations and stereochemistry are critically important to their reactivity. The abundance of cyclohexane rings in nature is probably due to both their stability and the selectivity offered by their predictable conformations.

The combustion data (Table 4−4) shows that cyclohexane has *no* ring strain. Cyclohexane must have bond angles that are near the tetrahedral angle (no angle strain) and also have no eclipsing of bonds (no torsional strain). A planar, regular hexagon would have bond angles of 120° rather than 109.5°, implying some angle strain. A planar ring would also have torsional strain because the bonds on adjacent CH_2 groups would be

eclipsed. Therefore, the cyclohexane ring cannot be planar.

4-6A Chair and Boat Conformations

Cyclohexane achieves tetrahedral bond angles and staggered conformations by assuming a puckered conformation. The most stable conformation is the **chair conformation** shown in Figure 4-13. Build a molecular model of cyclohexane, and compare its shape with the drawings in Figure 4-13. In the chair conformation, the angles between the carbon-carbon bonds are all 109.5°. The Newman projection looking down the "seat" bonds shows all the bonds in staggered conformations.

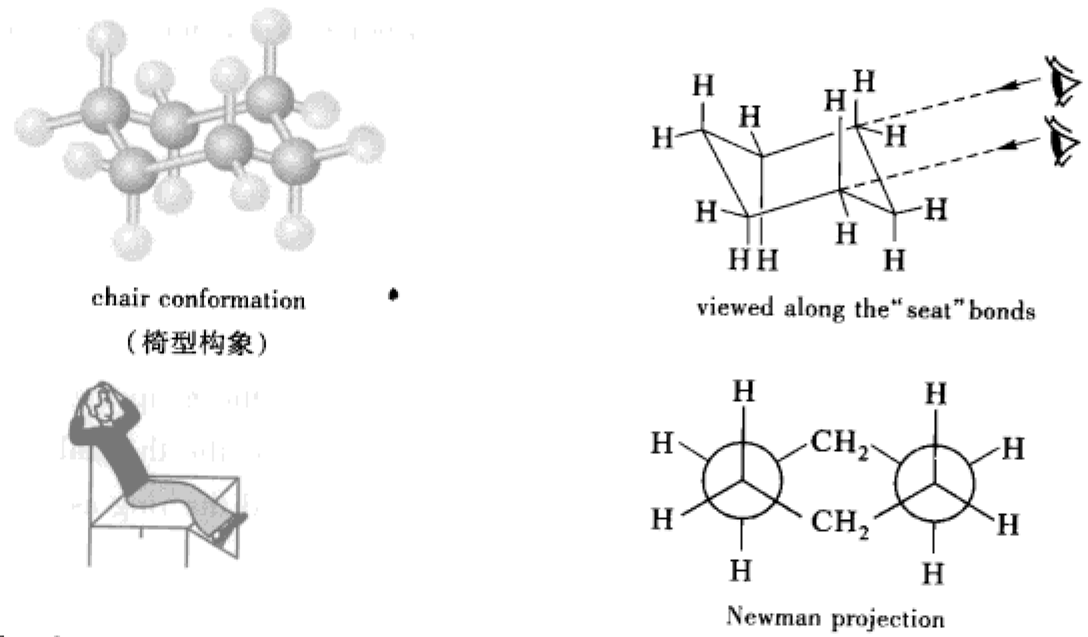


Figure 4-13 The chair conformation of cyclohexane has one methylene group puckered upward and another puckered downward. Viewed from the Newman projection, the chair has no eclipsing of the carbon-carbon bonds. The bond angles are 109.5°.

The **boat conformation** of cyclohexane (Figure 4-14) also has bond angles of 109.5° and avoids angle strain. The boat conformation resembles the chair conformation except that the "footrest" methylene group is folded upward. The boat conformation suffers from torsional strain, however, because there is eclipsing of bonds.

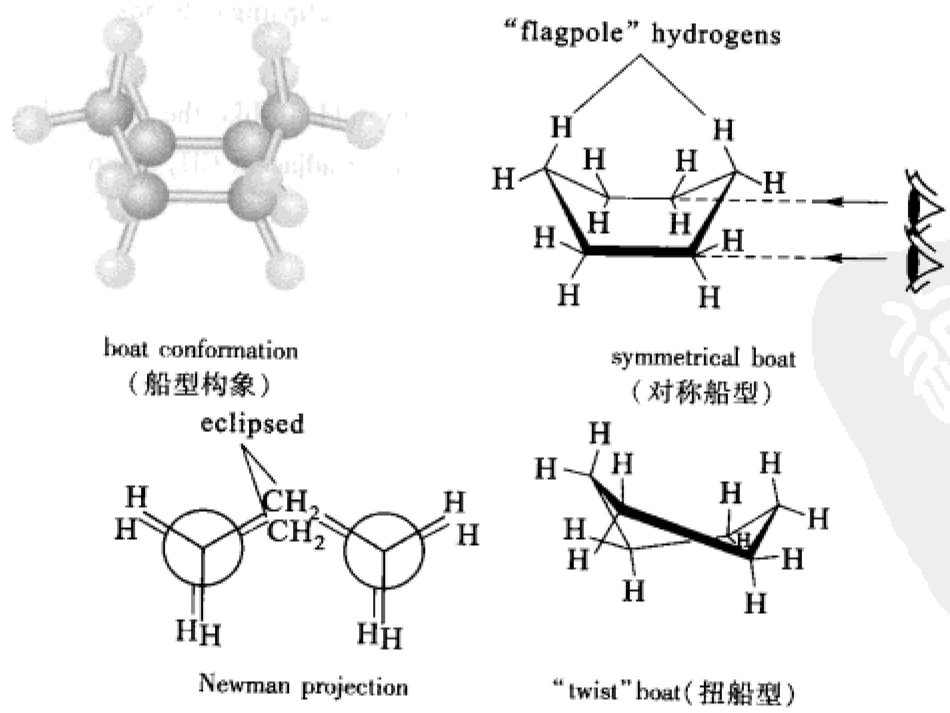


Figure 4-14 In the symmetrical boat conformation of cyclohexane, eclipsing of bonds results in torsional strain. In the actual molecule, the boat is skewed to give the twist boat, a conformation with less eclipsing of bonds and less interference between the two flagpole hydrogens.

This eclipsing forces two of the hydrogens on the ends of the "boat" to interfere with each other. These hydrogens are called **flagpole hydrogens** because they point upward from the ends of the boat like two flagpoles. The Newman projection in Figure 4-14 shows this eclipsing of the carbon-carbon bonds along the sides of the boat.

A cyclohexane molecule in the boat conformation actually exists as a slightly skewed **twist boat conformation**, also shown in Figure 4-14. If you assemble your molecular model in the boat conformation and twist it slightly, the flagpole hydrogens move away from each other and the eclipsing of the bonds is reduced. Even though the twist boat is lower in energy than the symmetrical boat, it is still about 23 kJ/mol higher in energy than the chair conformation. When someone refers to the "boat conformation," the twist boat (or simply **twist**) conformation is often intended.

At any instant, most of the molecules in a cyclohexane sample are in chair conformations. The energy barrier between the boat and chair is sufficiently low, however, that the conformations interconvert many times each second. The interconversion from the chair to the boat takes place by the footrest of the chair flipping upward and forming the boat. The highest-energy point in this process is the conformation where the footrest is planar with the sides of the molecule. This unstable arrangement is called the **half-chair conformation**. Figure 4-15 shows how the energy of cyclohexane varies as it interconverts between the boat and chair forms.

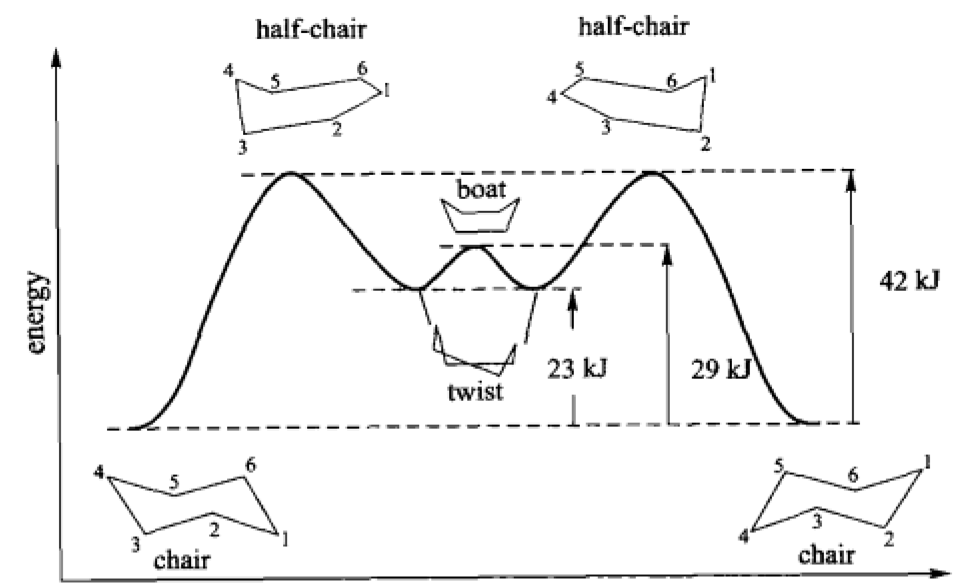


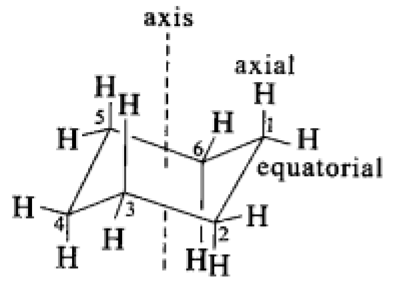
Figure 4-15 Conformational energy of cyclohexane. The chair conformation is most stable, followed by the twist boat. To convert between these two conformations, the molecule must pass through the unstable half-chair conformation.

4-6B Axial and Equatorial Positions

If we could freeze cyclohexane in the chair conformation, we would see that there are two different kinds of carbon-hydrogen bonds. Six of the bonds (one on each carbon atom) are directed up and down, parallel to the axis of the ring. These are called **axial bonds**. The other six bonds point out from the ring, along the "equator" of the ring. These are called **equatorial bonds**.

Each carbon atom in cyclohexane is bonded to two hydrogen atoms, one directed upward and one downward. As the carbon atoms are numbered in Figure 4-16, C1 has an axial bond upward and an equatorial bond downward. C2 has an equatorial bond upward and an axial bond downward. The pattern alternates. The odd-numbered carbon atoms have axial bonds up and equatorial bonds down, like C1. The even-numbered carbons have equatorial bonds up and axial bonds down, like C2. This pattern of alternating axial and equatorial bonds is

helpful for predicting the conformations of substituted cyclohexanes.



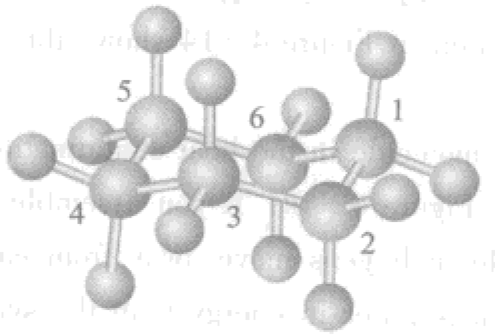


Figure 4−16 Axial bonds are directed vertically, parallel to the axis of the ring. Equatorial bonds are directed outward, toward the equator of the ring. As they are numbered here, the odd-numbered carbons have their *upward* bonds axial and their *downward* bonds equatorial. The even-numbered carbons have their *downward* bonds axial and their *upward* bonds equatorial.

PROBLEM 4−4

Draw 1,2,3,4,5,6-hexamethylcyclohexane with all the methyl groups
(a) in axial positions. **(b)** in equatorial positions.

4−7 Conformations of Monosubstituted Cyclohexanes

A substituent on a cyclohexane ring (in the chair conformation) can occupy either an axial or an equatorial position. In many cases, the reactivity of the substituent depends on whether its position is axial or equatorial. The two possible chair conformations for methylcyclohexane are shown in Figure 4−17. These conformations are in equilibrium because they interconvert at room temperature. The twist boat serves as an intermediate in this **chair-chair interconversion**, sometimes called a "ring-flip." Place different-colored atoms in the axial and equatorial positions of your cyclohexane model, and notice that the chair-chair interconversion changes axial to equatorial and equatorial to axial.

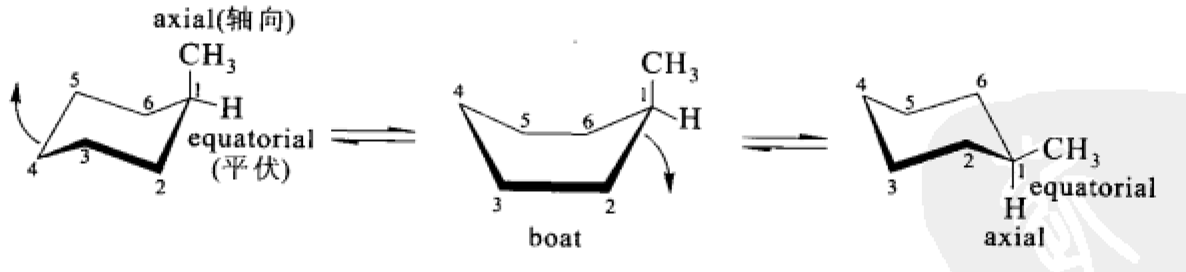


Figure 4−17 Chair-chair interconversion of methylcyclohexane. The methyl group is axial in one conformation, and equatorial in the other.

The two chair conformations of methylcyclohexane interconvert at room temperature, so the one that is lower in energy predominates. Careful measurements have shown that the chair with the methyl group in an equatorial position is the most stable conformation. It is about 7.6 kJ/mol lower in energy than the conformation with the methyl group in an axial position. Both of these chair conformations are lower in energy than any boat conformation. We can show how the 7.6 kJ energy difference between the axial and equatorial positions arises by examining molecular models and Newman projections of the two conformations. First, make a model of methylcyclohexane

and use it to follow this discussion.

Consider a Newman projection looking along the armrest bonds of the conformation with the methyl group axial (Figure 4-18a): The methyl group is on C1, and we are looking from C1 toward C2. There is a 60° angle between the bond to the methyl group and the bond from C2 to C3, and the methyl substituent and C3 are in a gauche relationship. In our analysis of torsional strain in butane, we saw that a gauche interaction raises the energy of a conformation by 3.8 kJ/mol relative to the anti conformation. This axial methyl group is also gauche to C5, as you will see if you look along the C1—C6 bond in your model. Figure 4-18b shows this second gauche relationship.

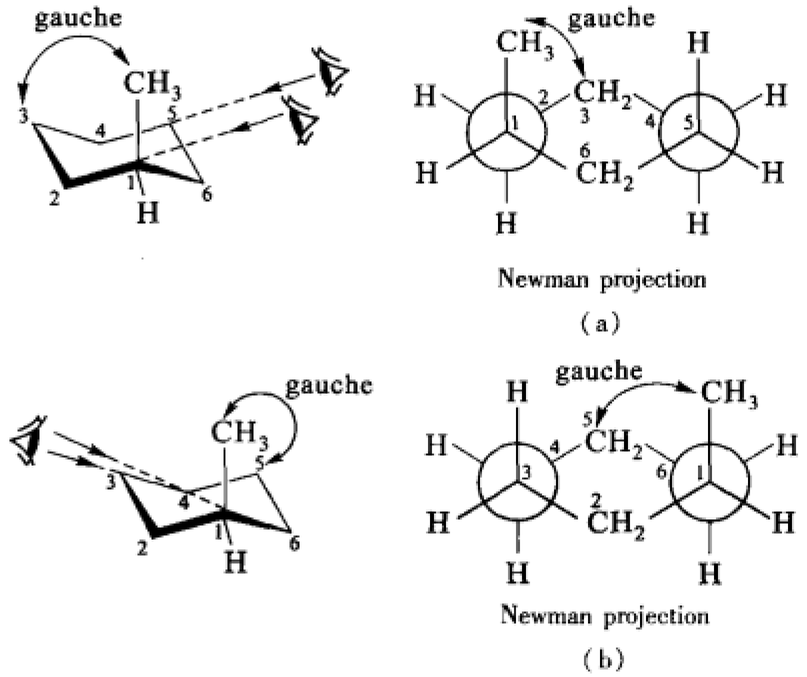


Figure 4-18 (a) When the methyl substituent is in an axial position on C1, it is gauche to C3.
(b) The axial methyl group on C1 is also gauche to C5 of the ring.

The Newman projection for the conformation with the methyl group equatorial shows that the methyl group has an anti relationship to both C3 and C5. Figure 4-19 shows the Newman projection along the C1—C2 bond, with the anti relationship of the methyl group to C3.

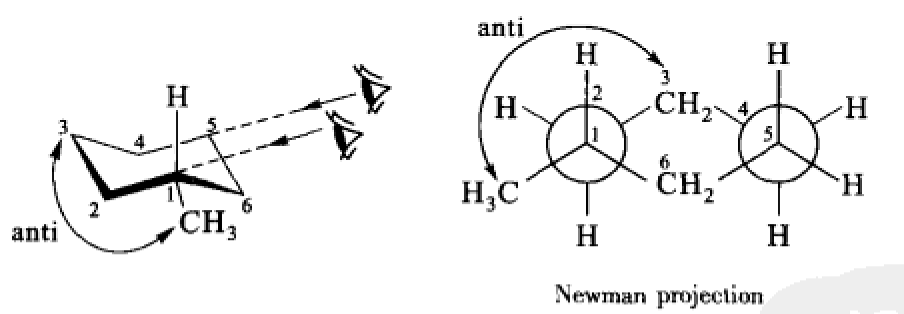


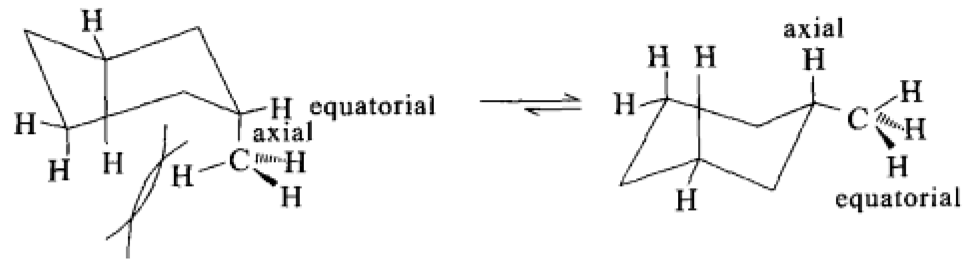
Figure 4-19 Looking down the C1—C2 bond of the equatorial conformation. Notice that the methyl group is anti to C3.

PROBLEM 4-5

Draw a Newman projection, similar to Figure 4-19, down the C1—C6 bond in the equatorial conformation of methylcyclohexane. Show that the equatorial methyl group is also anti to C5.

The axial methylcyclohexane conformation has two gauche interactions, each representing about 3.8 kJ of additional energy. The equatorial methyl group has no gauche interactions. Therefore, we predict that the axial conformation is higher in energy by 7.6 kJ per mole, in good agreement with the experimental value. Figure 4-20 shows that the gauche relationship of the axial methyl group with C3 and C5 places the methyl hydrogens

close to the axial hydrogens on these carbons, and their electron clouds begin to interfere. This form of steric hindrance is called a **1,3-diaxial interaction** because it involves substituents on the carbon atom that would be numbered C3 if the carbon bearing the methyl group was numbered C1. These 1,3-diaxial interactions are not present in the equatorial conformation.

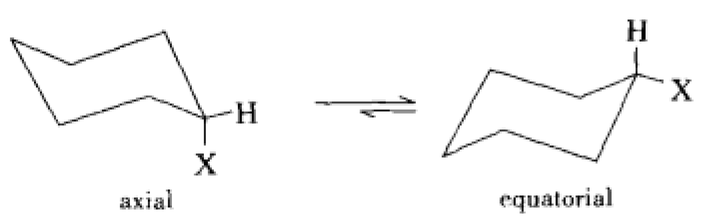


1,3-diaxial interactions　　　　more stable by 7.1 kJ/mol

Figure 4−20 The axial substituent interferes with the axial hydrogens on C3 and C5. This interference is called a 1,3-diaxial interaction.

A larger group usually has a larger energy difference between the axial and equatorial positions, because the 1,3-diaxial interaction shown in Figure 4−20 is stronger for larger groups. Table 4−5 shows the energy differences between the axial and equatorial positions for several alkyl groups and functional groups. The axial position is higher in energy in each case.

TABLE 4-5 Energy Differences Between the Axial and Equatorial Conformations of Monosubstituted Cyclohexanes



X	ΔG(axial-equatorial) /(kJ·mol^{-1})
—F	0.8
—CN	0.8
—Cl	2.1
—Br	2.5
—OH	4.1
—COOH	5.9
$—CH_3$	7.6
$—CH_2CH_3$	7.9
$—CH(CH_3)_2$	8.8
$—C(CH_3)_3$	23

PROBLEM 4−6

Table 4−5 shows that the axial-equatorial energy difference for methyl, ethyl, and isopropyl groups increases gradually: 7.6, 7.9, and 8.8 kJ/mol. The *t*-butyl group jumps to an energy difference of 23 kJ/mol, over twice the value for the isopropyl group. Draw pictures of the axial conformations of isopropylcyclohexane and *t*-butylcyclohexane, and explain why the *t*-butyl substituent experiences such a large increase in axial energy over the isopropyl group.

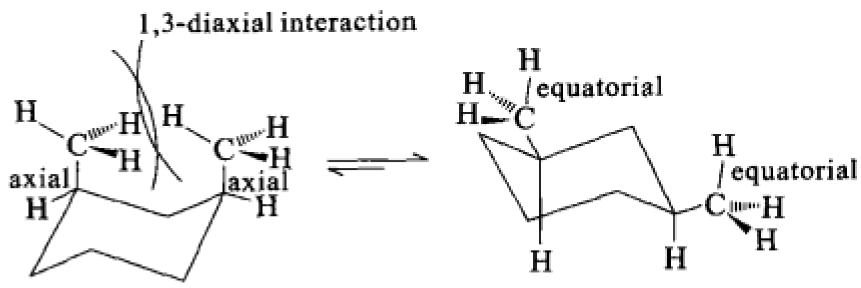
PROBLEM 4−7

Draw the most stable conformation of

(**a**) ethylcyclohexane（乙基环己烷）　(**b**) isopropylcyclohexane（异丙基环己烷）　(**c**) *t*-butylcyclohexane（叔丁基环己烷）

4-8 Conformations of Disubstituted Cyclohexanes

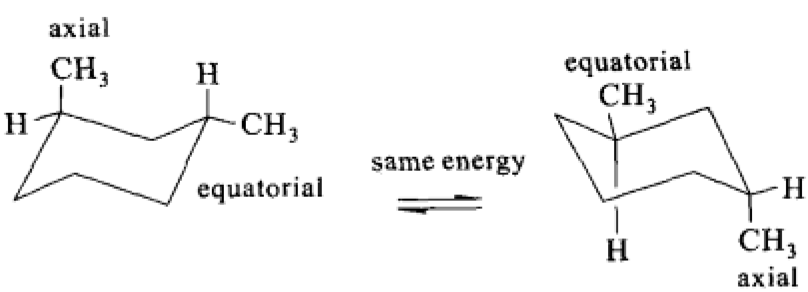
The steric interference between substituents in axial positions is particularly severe when there are large groups on two carbon atoms that bear a 1,3-diaxial relationship (*cis* on C1 and C3, or C1 and C5), as in the two chair conformations of *cis*-1,3-dimethylcyclohexane shown here. The less stable conformation has both methyl groups in axial positions. The more stable conformation has both methyl groups in equatorial positions. Note the strongly unfavorable 1,3-diaxial interaction between the two methyl groups in the diaxial conformation. The molecule can relieve this 1,3-diaxial interference by flipping to the diequatorial conformation. Use your models to compare the diaxial and diequatorial forms of *cis*-1,3-dimethylcyclohexane.



diaxial—very unfavorable (双轴向)　　diequatorial—much more stable (双平伏)

Either of the chair conformations of *trans*-1,3-dimethylcyclohexane has one methyl group in an axial position and one in an equatorial position. These conformations have equal energies, and they are present in equal amounts.

Chair conformations of trans-1,3-*dimethylcyclohexane*



Now we can compare the relative stabilities of the cis and trans isomers of 1,3-dimethylcyclohexane. The most stable conformation of the cis isomer has both methyl groups in equatorial positions. Either conformation of the trans isomer places one methyl group in an axial position. The trans isomer is therefore higher in energy than the cis isomer by about 7.6 kJ/mol, the energy difference between axial and equatorial methyl groups. Remember that the cis and trans isomers cannot interconvert, and there is no equilibrium between these isomers.

SOLVED PROBLEM 4-1

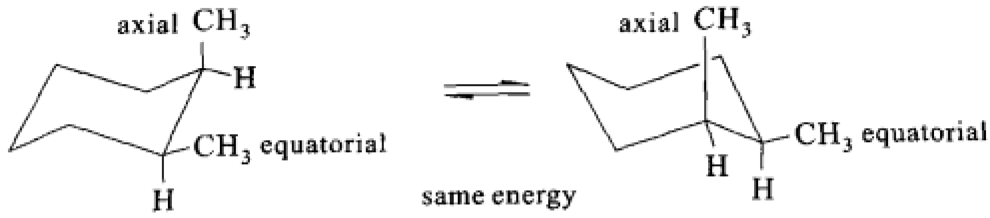
(**a**) Draw both chair conformations of *cis*-1,2-dimethylcyclohexane, and determine which conformer is more stable.

(**b**) Repeat for the trans isomer.

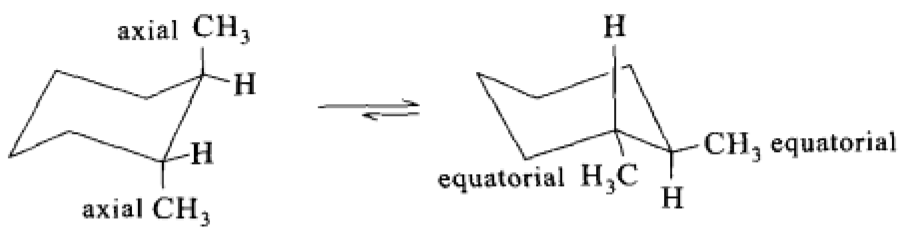
(**c**) Predict which isomer (cis or trans) is more stable.

SOLUTION

(**a**) There are two possible chair conformations for the cis isomer, and these two conformations interconvert at room temperature. Each of these conformations places one methyl group axial and one equatorial, giving them the same energy.



(b) There are two chair conformations of the trans isomer that interconvert at room temperature. Both methyl groups are axial in one, and both are equatorial in the other. The diequatorial conformation is more stable because neither methyl group occupies the more hindered axial position.



(c) The trans isomer is more stable. The most stable conformation of the trans isomer is diequatorial and therefore about 7.6 kJ/mol lower in energy than either conformation of the cis isomer, each having one methyl axial and one equatorial. Remember that cis and trans are distinct isomers and cannot interconvert.

PROBLEM 4-8

(a) Draw both chair conformations of *cis*-1,4-dimethylcyclohexane, and determine which conformer is more stable.

(b) Repeat for the trans isomer.

(c) Predict which isomer (cis or trans) is more stable.

PROBLEM 4-9

Use your results from Problem 4-8 to complete the following table. Each entry shows the positions of two groups arranged as shown. For example, two groups that are trans on adjacent carbons (*trans*-1,2) must be both equatorial (e,e) or both axial (a,a).

Positions	cis	trans
1,2	(e,a) or (a,e)	(e,e) or (a,a)
1,3		
1,4		

4-8A Substituents of Different Sizes

In many substituted cyclohexanes, the substituents are different sizes. As shown in Table 4-5, the energy difference between the axial and equatorial positions for a larger group is greater than that for a smaller group. In general, if both groups cannot be equatorial, the most stable conformation has the larger group equatorial and the smaller group axial.

PROBLEM 4-10

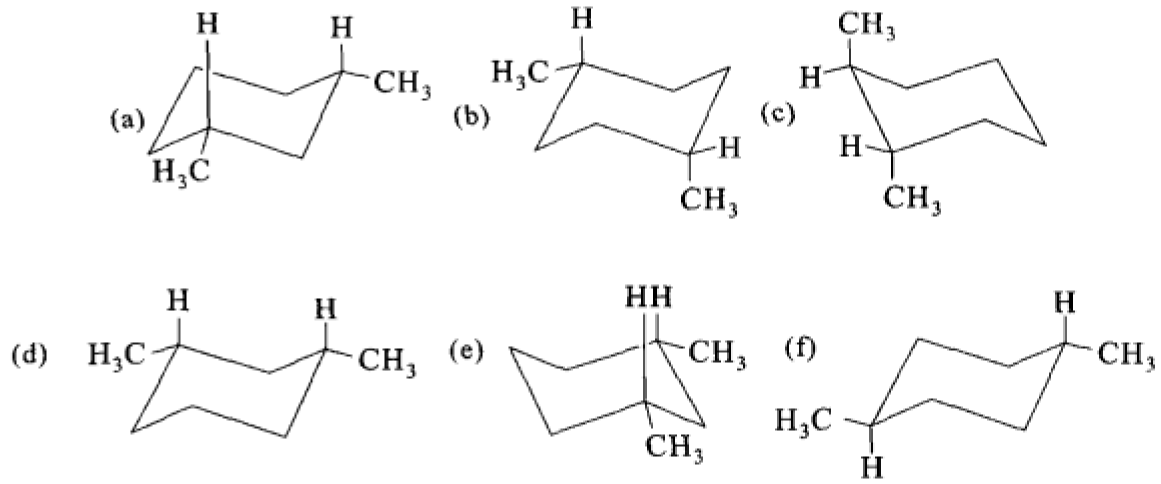
Draw the two chair conformations of each of the following substituted cyclohexanes. In each case, label the more stable conformation.

(a) *cis*-1-ethyl-2-methylcyclohexane **(b)** *trans*-1-ethyl-2-methylcyclohexane

(c) *cis*-1-ethyl-4-isopropylcyclohexane (d) *trans*-1-ethyl-4-methylcyclohexane

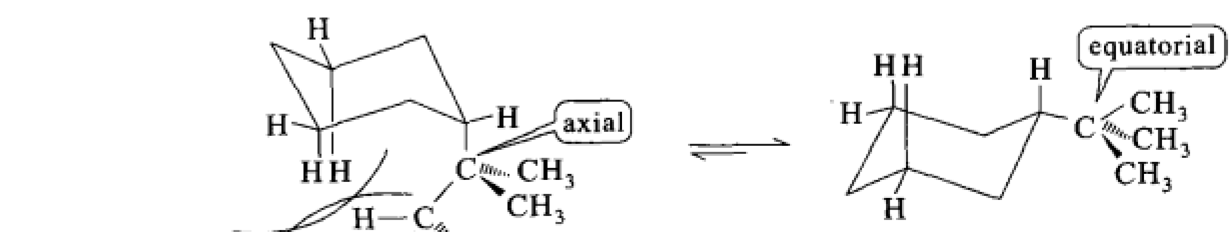
PROBLEM 4-11

Name the following compounds. Remember that two *up* bonds are cis; two *down* bonds are cis; one *up* bond and one *down* bond are trans.



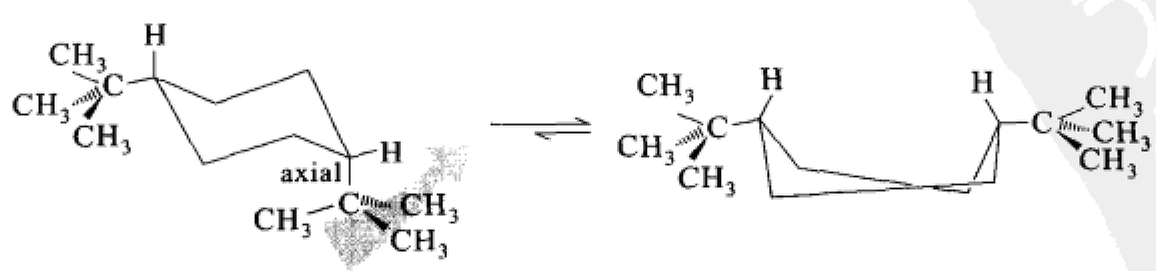
4-8B Extremely Bulky Groups

Some groups, such as *tertiary*-butyl groups, are so bulky that they are extremely strained in axial positions. Regardless of the other groups present, cyclohexanes with t-butyl substituents are most stable when the t-butyl group is in an equatorial position. The following figure shows the severe steric interactions in a chair conformation with a t-butyl group axial.



strongly preferred conformation

If two t-butyl groups are attached to the ring, both of them are much less strained in equatorial positions. When neither chair conformation allows both bulky groups to be equatorial, they may force the ring into a twist boat conformation. For example, either chair conformation of *cis*-1,4-di-t-butylcyclohexane requires one of the bulky t-butyl groups to occupy an axial position. This compound is more stable in a twist boat conformation that allows both bulky groups to avoid axial positions.



t-butyl group moves out of the axial position twist boat

PROBLEM 4-12

Draw the most stable conformation of

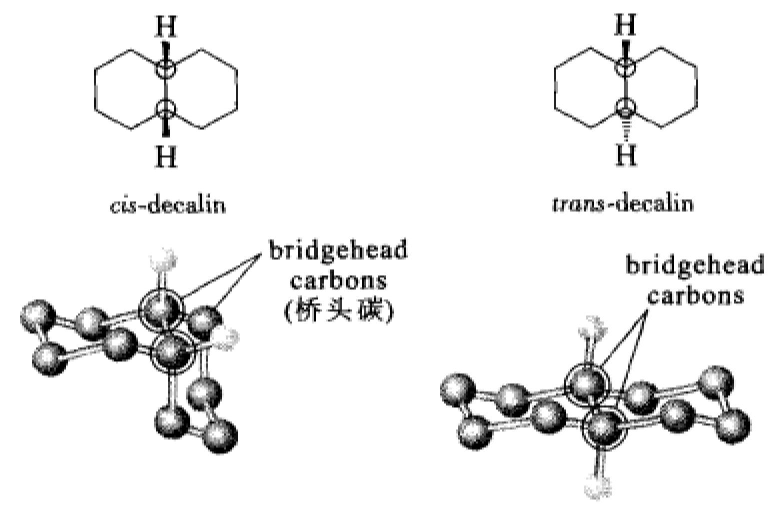
(a) *cis*-1-*t*-butyl-3-ethylcyclohexane

(b) *trans*-1-*t*-butyl-2-methylcyclohexane

(c) *trans*-1-*t*-butyl-3-(1,1-dimethylpropyl) cyclohexane

4-8C *cis*-and *trans*-Decalin

Decalin (bicyclo [4. 4. 0] decane) is the most common example of a fused-ring system. Two geometric isomers of decalin exist, as shown in Figure 4-21. In one isomer the rings are fused using two cis bonds, while the other is fused using two trans bonds. You should make a model of decalin to follow this discussion.



cis-decalin (顺-十氢化萘) *trans*-decalin (反-十氢化萘)

Figure 4-21 *cis*-Decalin has a ring fusion where the second ring is attached by two cis bonds. *trans*-Decalin is fused using two trans bonds. (The other hydrogens are omitted for clarity.)

If we consider the left ring in the drawing of *cis*-decalin, the bonds to the right ring are both directed downward (and the attached hydrogens are directed upward). These bonds are therefore cis ,and this is a cis ring fusion. In *trans*-decalin, one of the bonds to the right ring is directed upward and the other downward. These bonds are trans, and this is a trans ring fusion. The six-membered rings in both isomers assume chair conformations, as shown in Figure 4-21. The conformation of *cis*-decalin is somewhat flexible, but the trans isomer is quite rigid. If one of the rings in the trans isomer did a chair-chair interconversion, the bonds to the second ring would both become axial and would be directed 180° apart. This is an impossible conformation, and it prevents any chair-chair interconversion in *trans*-decalin.

Summary in Chinese

本 章 概 要

一、烷烃 (alkanes)

分子中碳原子都是以单键键合的烃称为饱和烃或烷烃，可分为链烷烃(C_nH_{2n+2})、环烷烃(C_nH_{2n})和双环烷烃(包括螺环和桥环)。分子式相差 CH_2 的同一类化合物称为同系物(homologs)。烷烃的主要来源为天然气和石油。

二、烷烃的物理性质（physical property of alkanes）

烷烃为非极性分子，具有疏水性，相对密度均小于1。正构烷烃的沸点和熔点均随相对分子质量增加而有规律地升高。烷烃的同分异构体中，正构烷烃沸点最高，含支链越多的烷烃沸点越低。一般支链烷烃的熔点比相对分子质量相同的正构烷烃的低，但当支链烷烃分子具有良好的对称性时，其熔点高于同碳数正构烷烃。

三、烷烃的化学反应（chemical reactions of alkanes）

烷烃无官能团，化学性质稳定，常温下不易反应，但在光或热作用下，具有自由基型反应性能。

1. 完全氧化反应（combustion）：烷烃燃烧时被完全氧化生成 CO_2 和 H_2O，反应大量放热。烷烃的主要用途之一是作为燃料。通常以辛烷值（octane number）衡量汽油混合物燃烧时的抗震性能。

2. 裂解及氢化裂解反应（cracking and hydrocracking）：大分子烷烃在无空气存在下热分解生成小分子烷烃和烯烃的反应称为裂解反应。大分子烷烃在氢气存在下热裂解生成小分子烷烃的反应称为氢化裂解反应，烷烃裂解反应是炼油工业的基本反应。

3. 卤代反应（halogenation）：在光或热引发下，烷烃可与卤素反应生成卤代烷，是合成卤代烷的方法之一（Chapter 5 and Section 7-5）。

四、烷烃的构象（conformation of alkanes）

1. 构象异构体（conformer）：分子中原子或基团通过绕单键旋转而产生的空间排列方式不同的结构称为构象异构体。构象异构体不是真正的异构体，大多数情况下，构象异构体在室温下可通过单键旋转，快速相互转变。分子构象可用锯架式（sawhorse structure）或纽曼投影式（Newman projection）表示。

2. 构象式稳定性：重叠式构象（eclipsed conformation）和交叉式构象（staggered conformation）是构象分析考虑的两种极限构象。在交叉式中空间相邻的原子相互间距离最远，原子与原子相互间空间张力（steric strain）最小，使成键电子相互间排斥力达到最小，此时，键的扭转张力（torsional strain）最小。因此，交叉式构象的稳定性远大于重叠式构象。对于 C_4 以上烷烃进行构象分析时，应考虑全重叠式、顺交叉式、部分重叠式和反交叉式四种极限构象。比较各种构象中两个大基团间的空间张力（范德华斥力）和成键电子对相互间的排斥力大小，可以得到各种构象的相对能量变化曲线。四种构象稳定性顺序为：反交叉式 > 顺交叉式 > 部分重叠式 > 全重叠式。当两个相邻碳原子上的原子或基团处于顺交叉式能形成氢键时，顺交叉式为最稳定构象。

五、环烷烃（cycloalkanes）

1. 环烷烃的性质：环烷烃具有与烷烃相似的物理性质。一般来说，环烷烃的沸点、熔点和相对密度均高于同碳数的正构烷烃。环烷烃的通式为 C_nH_{2n}，与烯烃互为构造异构体，但除 C_3 和 C_4 小分子环烷烃能发生加成开环反应外，环烷烃具有与链烷烃相似的化学性质，如在光或热作用下可发生自由基型反应。

2. 环烷烃的稳定性：环烷烃具有环张力。环张力（ring strain）= 角张力（angle strain）+ 扭转张力（torsional strain）。通过测量环烷烃的燃烧热可估算出各种环烷烃的环张力。$C_3 \sim C_6$ 环烷烃的环张力顺序为：环丙烷 > 环丁烷 > 环戊烷 > 环己烷，稳定性顺序与环张力顺序相反。大于6个碳的环烷烃柔性好，环张力小，稳定性好。

3. 环烷烃的构象：环丁烷的稳定构象为蝴蝶型构象（butterfly conformation），环戊烷为信封型构象（envelope conformation），环己烷为椅型构象（chair conformation）。除了最稳定的椅型构象外，环己烷的其他可能构象为：扭转型（twist）、船型（boat）和半椅型（half chair），稳定性顺序递减。这些构象之间可以通过环的扭动相互转变。在环己烷椅型构象中，与环相连的十二个 C—H 键可分为两组，与环的平均平面垂直的六个 C—H 键称为直立键（axial bonds），而与该平面接近平行的六个 C—H 键称为平伏键（equatorial bonds）。除特殊情况外（如直立键上的原子或基团间形成分子内氢键等），判断取代环己烷构象稳定性的原则是：环上体积大的取代基位于平伏键的椅型构象比其位于直立键的椅型构象稳定。取代基体积越大，两种椅型构象的能量差越大，导致稳定构象所占比例越大。环己烷的构象对其化学反应性质和机理有重要影响。

Essential Problem-Solving Skills in Chapter 4

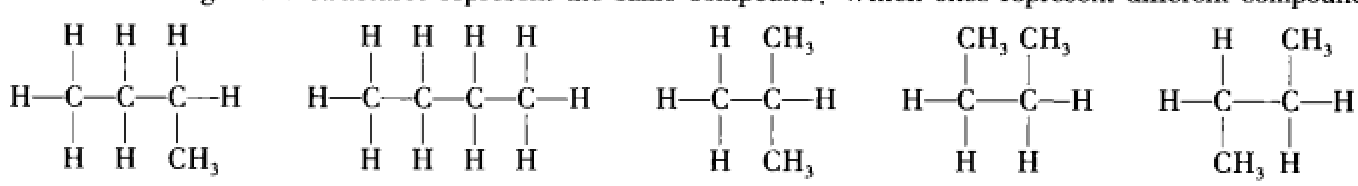
1. Explain and predict trends in physical properties of alkanes.
2. Compare the energies of alkane conformations and predict the most stable conformation.
3. Compare the energies of cycloalkanes, and explain ring strain.
4. Identify and draw cis and trans stereoisomers of cycloalkanes.
5. Draw accurate cyclohexane conformations, and predict the most stable conformations of substituted cyclohexanes.

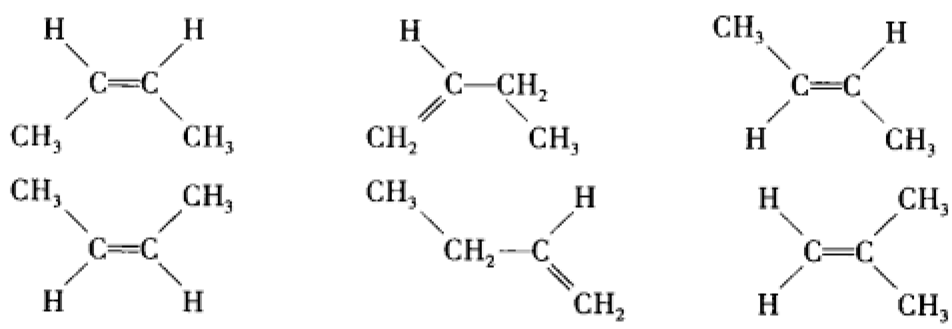
Study Problems

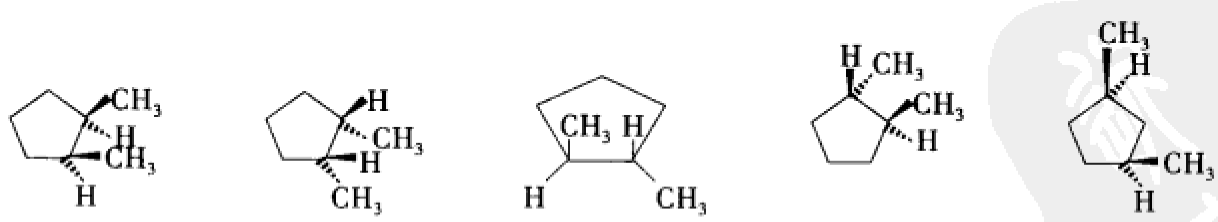
4-13 Define and give an example for each term.

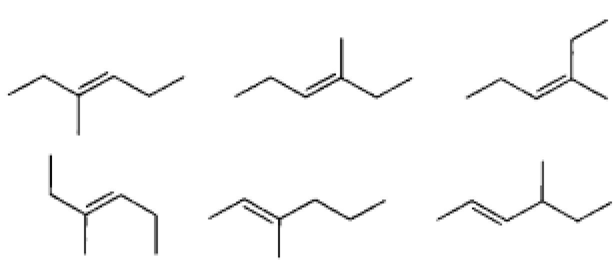
(a) conformers（构象异构体）
(b) eclipsed（重叠的）
(c) Newman projection（纽曼投影式）
(d) staggered（交叉的）
(e) gauche（顺交叉的）
(f) anti conformation（反式构象）
(g) an acyclic alkane（非环烷烃）
(h) cis-trans isomers on a ring
(i) chair conformation（椅型构象）
(j) boat conformation（船型构象）
(k) twist boat（扭船型）
(l) half-chair conformation（半椅型构象）
(m) axial position（轴向位置）
(n) equatorial position（平伏位置）
(o) catalytic cracking（催化裂化）
(p) chair-chair interconversion（椅-椅互变）
(q) fused ring system（稠环体系）
(r) bridged bicyclic compound（桥双环化合物）
(s) bridgehead carbon atoms（桥头碳原子）
(t) combustion（燃烧）

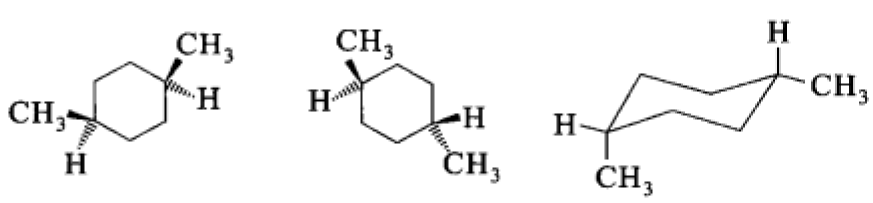
4-14 Which of the following Lewis structures represent the same compound? Which ones represent different compounds?

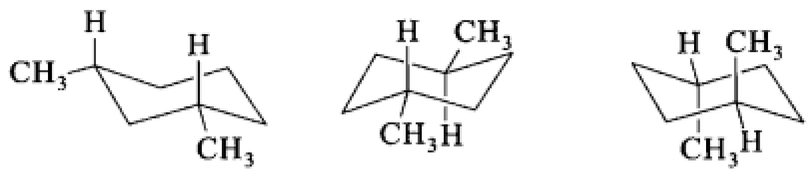
(a) 

(b) 

(c) 

(d) 

(e) 



4-15 In each pair of compounds, which compound has the higher boiling point? Explain your reasoning.

(**a**) octane or 2,2,3-trimethylpentane (**b**) heptane or 2-methylnonane

(**c**) 2,2,5-trimethylhexane or nonane

4-16 Use a Newman projection, about the indicated bond, to draw the most stable conformer for each compound.

(**a**) 3-methylpentane about the C2—C3 bond (**b**) 3,3-dimethylhexane about the C3—C4 bond

4-17 (**a**) Draw the two chair conformations of *cis*-1,3-dimethylcyclohexane, and label all the positions as axial or equatorial.

(**b**) Label the higher-energy conformation and the lower-energy conformation.

(**c**) The energy difference in these two conformations has been measured to be about 23 kJ per mole. How much of this energy difference is due to the torsional energy of gauche relationships?

(**d**) How much energy is due to the additional steric strain of the 1,3-diaxial interaction?

4-18 Draw the two chair conformations of each compound, and label the substituents as axial and equatorial. In each case, determine which conformation is more stable.

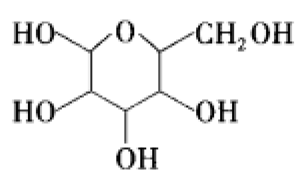
(**a**) *cis*-1-ethyl-2-isopropylcyclohexane (**b**) *trans*-1-ethyl-2-isopropylcyclohexane

(**c**) *cis*-1-ethyl-3-methylcyclohexane (**d**) *trans*-1-ethyl-3-methylcyclohexane

(**e**) *cis*-1-ethyl-4-methylcyclohexane

4-19 Using what you know about the conformational energetics of substituted cyclohexanes, predict which of the two decalin isomers is more stable. Explain your reasoning.

4-20 The most stable form of the common sugar glucose contains a six-membered ring in the chair conformation with all the substituents equatorial. Draw this most stable conformation of glucose.



glucose (葡萄糖)

Chapter 5
The Study of Chemical Reactions

5–1 Introduction

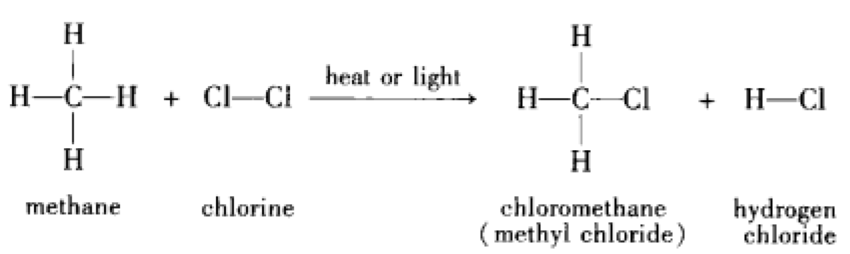
The most interesting and useful aspect of organic chemistry is the study of reactions. We cannot remember thousands of specific organic reactions, but we can organize the reactions into logical groups based on how the reactions take place and what intermediates are involved. We begin our study by considering the *halogenation* of alkanes, a relatively simple reaction that takes place in the gas phase, without a solvent to complicate the reaction. In practice, alkanes are so unreactive that they are rarely used as starting materials for most organic syntheses. We start with them because we have already studied their structure and properties, and their reactions are relatively uncomplicated. Once we have used alkanes to introduce the tools for studying reactions, we will apply those tools to a variety of more useful reactions.

The overall reaction, with the reactants on the left and the products on the right, is only the first step in our study of a reaction. If we truly want to understand a reaction, we must also know the **mechanism**, the step-by-step pathway from reactants to products. To know how well the reaction goes to products, we study its **thermodynamics**, the energetics of the reaction at equilibrium. The amounts of reactants and products present at equilibrium depend on their relative stabilities.

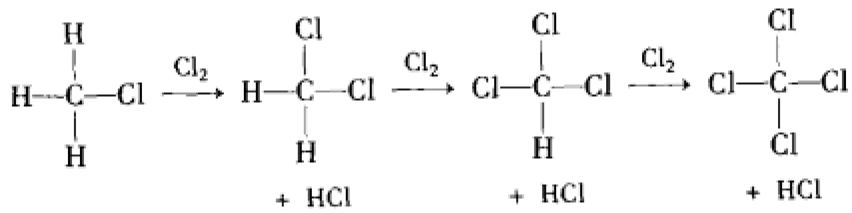
Even though the equilibrium may favor the formation of a product, the reaction may not take place at a useful rate. To use a reaction in a realistic time period (and to keep the reaction from becoming violent), we study its **kinetics**, the variation of reaction rates with different conditions and concentrations of reagents. Understanding the reaction's kinetics helps us to propose reaction mechanisms that are consistent with the properties we observe.

5–2 Chlorination of Methane

The reaction of methane with chlorine produces a mixture of chlorinated products, whose composition depends on the amount of chlorine added and also on the reaction conditions. Either light or heat is needed for the reaction to take place at a useful rate. When chlorine is added to methane, the first reaction is



This reaction may continue; heat or light is needed for each step:



This sequence raises several questions about the chlorination of methane. Why is heat or light needed for the reaction to go? Why do we get a mixture of products? Is there any way to modify the reaction to get just one pure product? Are the observed products formed because they are the most stable products possible? Or are they favored because they are formed faster than any other products?

The answers to these questions involve three aspects of the reaction: the mechanism, the thermodynamics, and the kinetics.

1. The **mechanism** is the complete, step-by-step description of exactly which bonds break and which bonds form in what order to give the observed products.

2. **Thermodynamics** is the study of the energy changes that accompany chemical and physical transformations. It allows us to compare the stability of reactants and products and predict which compounds are favored by the equilibrium.

3. **Kinetics** is the study of reaction rates, determining which products are formed fastest. Kinetics also helps to predict how the rate will change if we change the reaction conditions.

We will use the chlorination of methane to show how we study a reaction. Before we can propose a detailed mechanism for the chlorination, we must learn everything we can about how the reaction works and what factors affect the reaction rate and the product distribution.

A careful study of the chlorination of methane has established three important characteristics:

1. *The chlorination does not occur at room temperature in the absence of light.* The reaction begins when light falls on the mixture or when it is heated. Thus, we know this reaction requires some form of energy to *initiate* it.

2. *The most effective wavelength of light is a blue color that is strongly absorbed by chlorine gas.* This finding implies that light is absorbed by the chlorine molecule, activating chlorine so that it initiates the reaction with methane.

3. *The light-initiated reaction has a high quantum yield.* This means that many molecules of the product are formed for every photon of light absorbed. Our mechanism must explain how hundreds of individual reactions of methane with chlorine result from the absorption of a single photon by a single molecule of chlorine.

5-3 The Free-Radical Chain Reaction

A **chain reaction** mechanism has been proposed to explain the chlorination of methane. A chain reaction consists of three kinds of steps:

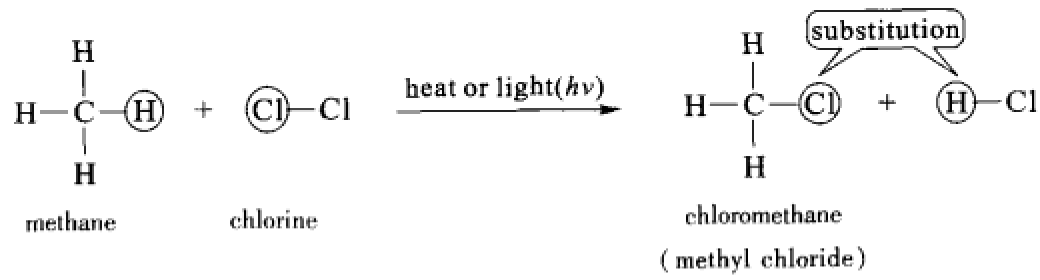
1. The **initiation step**, which generates a reactive intermediate.

2. **Propagation steps**, in which the reactive intermediate reacts with a stable molecule to form another reactive intermediate, allowing the chain to continue until the supply of reactants is exhausted or the reactive intermediate is destroyed.

3. **Termination steps**, side reactions that destroy reactive intermediates and tend to slow or stop the reaction.

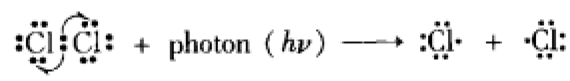
In studying the chlorination of methane, we will consider just the first reaction to form chloromethane (com-

mon name *methyl chloride*). This reaction is a **substitution**: Chlorine does not add to methane, but a chlorine atom *substitutes* for one of the hydrogen atoms, which becomes part of the HCl by-product.



5-3A The Initiation Step: Generation of Radicals

Blue light, absorbed by chlorine but not by methane, promotes this reaction. Therefore, initiation probably results from the absorption of light by a molecule of chlorine. Blue light has about the right energy to split a chlorine molecule (Cl_2) into two chlorine atoms (242 kJ/mol). The splitting of a chlorine molecule by absorption of a photon is shown as follows:



Notice the fishhook-shaped half-arrows used to show the movement of single unpaired electrons. Just as we use curved arrows to represent the movement of electron *pairs*, we use these curved half-arrows to represent the movement of single electrons. These half-arrows show that the two electrons in the Cl—Cl bond separate, and one leaves with each chlorine atom.

The splitting of a Cl_2 molecule is an initiation step that produces two highly reactive chlorine atoms. A chlorine atom is an example of a **reactive intermediate**, a short-lived species that is never present in high concentration because it reacts as quickly as it is formed. Each Cl· atom has an odd number of valence electrons (seven), one of which is unpaired. The unpaired electron is called the *odd electron* or the *radical electron*. Species with unpaired electrons are called **radicals** or **free radicals**. Radicals are electron-deficient because they lack an octet. The odd electron readily combines with an electron in another atom to complete an octet and form a bond. Figure 5-1 shows the Lewis structures of some free radicals. Radicals are often represented by a structure with a single dot representing the unpaired odd electron.

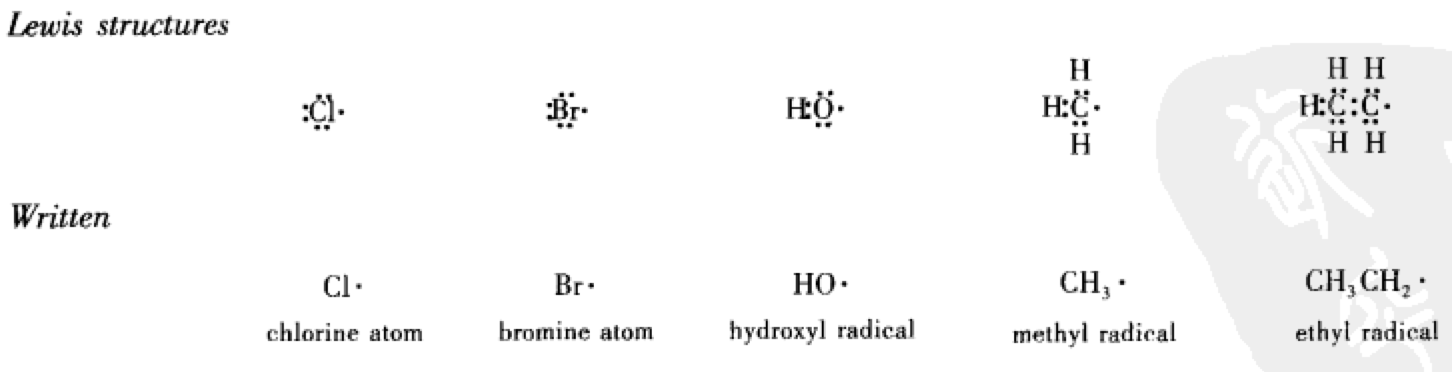


Figure 5-1 Free radicals. Free radicals are reactive species with odd numbers of electrons. The unpaired electron is represented by a dot in the formula.

5-3B Propagation Steps

When a chlorine radical collides with a methane molecule, it abstracts (removes) a hydrogen atom from methane. One of the electrons in the C—H bond remains on carbon while the other combines with the odd electron on the chlorine atom to form the H—Cl bond.

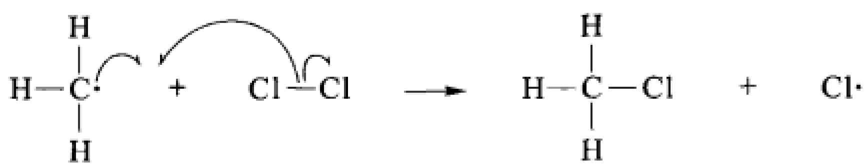
First propagation step

methane chlorine atom methyl radical hydrogen chloride

This step forms only one of the final products: the molecule of HCl. A later step must form chloromethane. Notice that the first propagation step begins with one free radical (the chlorine atom) and produces another free radical (the methyl radical). The regeneration of a free radical is characteristic of a propagation step of a chain reaction. The reaction can continue because another reactive intermediate is produced.

In the second propagation step, the methyl radical reacts with a molecule of chlorine to form chloromethane. The odd electron of the methyl radical combines with one of the two electrons in the Cl—Cl bond to give the Cl—CH_3 bond, and the chlorine atom is left with the odd electron.

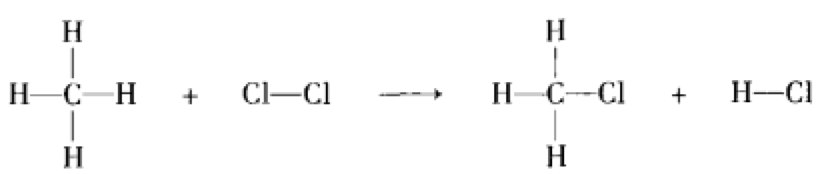
Second propagation step



methyl radical chlorine molecule chloromethane chlorine atom

In addition to forming chloromethane, the second propagation step produces another chlorine atom. The chlorine atom can react with another molecule of methane, giving HCl and a methyl radical, which reacts with Cl_2 to give chloromethane and regenerate yet another chlorine radical, which goes on to react in the first propagation step. In this way, the chain reaction continues until the supply of the reactants is exhausted or some other reaction consumes the radical intermediates. The chain reaction explains why many molecules of methyl chloride and HCl are formed by each photon of light that is absorbed.

The overall reaction is simply the sum of the propagation steps:



PROBLEM 5-1

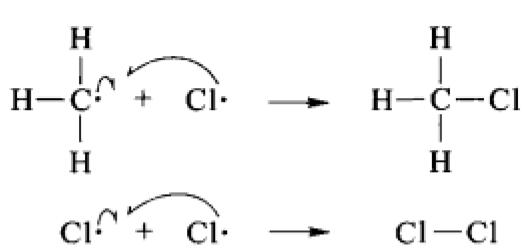
(a) Write the propagation steps leading to the formation of dichloromethane (CH_2Cl_2) from chloromethane.

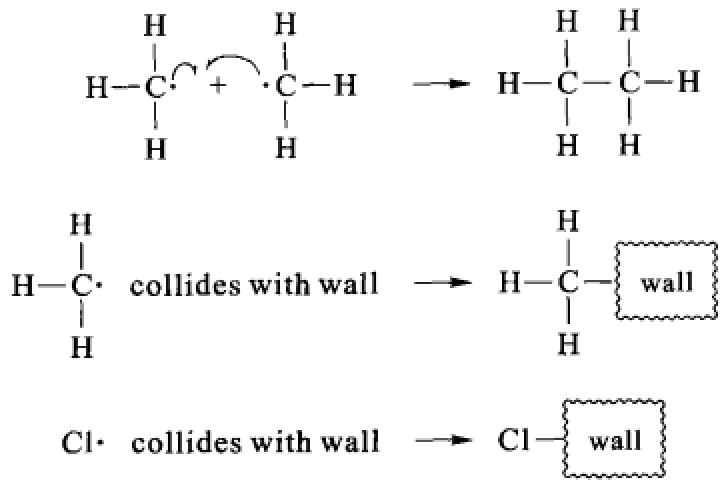
(b) Explain why free-radical halogenation usually gives mixtures of products.

(c) How could an industrial plant control the proportions of methane and chlorine to favor production of CCl_4? To favor CH_3Cl?

5-3C Termination Reactions

If anything happens to consume some of the free-radical intermediates without generating new ones, the chain reaction will slow or stop. Such a side reaction is called a **termination reaction**: a step that produces fewer reactive intermediates (free radicals) than it consumes. The following are some of the possible termination reactions in the chlorination of methane:





The combination of any two free radicals is a termination step because it decreases the number of free radicals. Other termination steps involve reactions of free radicals with the walls of the vessel or other contaminants. Although the first of these termination steps gives chloromethane, one of the products, it consumes the free radicals that are necessary for the reaction to continue, thus breaking the chain. Its contribution to the amount of product obtained from the reaction is small compared with the contribution of the propagation steps.

While a chain reaction is in progress, the concentration of radicals is very low. The probability that two radicals will combine in a termination step is lower than the probability that each will encounter a molecule of reactant and give a propagation step. The termination steps become important toward the end of the reaction, when there are relatively few molecules of reactants available. At this point, the free radicals are less likely to encounter a molecule of reactant than they are to encounter each other (or the wall of the container). The chain reaction quickly stops.

PROBLEM 5-2

Each of the following proposed mechanisms for the free-radical chlorination of methane is wrong. Explain how the experimental evidence disproves each mechanism.

(**a**) $Cl_2 + h\nu \longrightarrow Cl_2^{\bullet}$ (an "activated" form of Cl_2)

$Cl_2^{\bullet} + CH_4 \longrightarrow HCl + CH_3Cl$

(**b**) $CH_4 + h\nu \longrightarrow \cdot CH_3 + H\cdot$

$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$

$Cl\cdot + H\cdot \longrightarrow HCl$

5-4 Equilibrium Constants and Free Energy

Now that we have determined a mechanism for the chlorination of methane, we can consider the energetics of the individual steps. Let's begin by reviewing some of the principles needed for this discussion.

Thermodynamics is the branch of chemistry that deals with the energy changes accompanying chemical and physical transformations. These energy changes are most useful for describing the properties of systems at **equilibrium**. Let's review how energy and entropy variables describe an equilibrium.

The equilibrium concentrations of reactants and products are governed by the **equilibrium constant** of the reaction. For example, if A and B react to give C and D, then the equilibrium constant K_{eq} is defined by the following equation:

$$A + B \rightleftharpoons C + D$$

$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]} = \frac{[C][D]}{[A][B]}$$

The value of K_{eq} tells us the position of the equilibrium: whether the products or the reactants are more stable, and therefore energetically favored. If K_{eq} is larger than 1, the reaction is favored as written from left to right. If K_{eq} is less than 1, the reverse reaction is favored (from right to left as written).

The chlorination of methane has a large equilibrium constant of about 1.1×10^{19}.

$$CH_4 + Cl_2 \rightleftharpoons CH_3Cl + HCl$$

$$K_{eq} = \frac{[CH_3Cl][HCl]}{[CH_4][Cl_2]} = 1.1 \times 10^{19}$$

The equilibrium constant for chlorination is so large that the remaining amounts of the reactants are close to zero at equilibrium. Such a reaction is said to *go to completion*, and the value of K_{eq} is a measure of the reaction's tendency to go to completion.

From the value of K_{eq} we can calculate the change in **free energy** (sometimes called **Gibbs free energy**) that accompanies the reaction. Free energy is represented by G, and the change (Δ) in free energy associated with a reaction is represented by ΔG, the difference between the free energy of the products and the free energy of the reactants. ΔG is a measure of the amount of energy available to do work.

$$\Delta G = (\text{free energy of products}) - (\text{free energy of reactants})$$

If the energy levels of the products are lower than the energy levels of the reactants (a "downhill" reaction), then the reaction is energetically favored; and this equation gives a negative value of ΔG, corresponding to a decrease in the energy of the system.

The **standard Gibbs free energy change**, $\Delta G^\ominus$, is most commonly used. The symbol$^\ominus$ designates a reaction involving reactants and products in their standard states (pure substances in their most stable states at 25 ℃ and 1 atm pressure). The relationship between $\Delta G^\ominus$ and K_{eq} is given by the expression

$$K_{eq} = e^{-\Delta G^\ominus/(RT)}$$

or, conversely, by

$$\Delta G^\ominus = -RT(\ln K_{eq}) = -2.303\, RT(\lg K_{eq})$$

where

$R = 8.314$ J/(mol·K), the gas constant

T = absolute temperature, in kelvins①

e = 2.718, the base of natural logarithms

The value of RT at 25 ℃ is about 2.48 kJ/mol.

The formula shows that a reaction is favored ($K_{eq} > 1$) if it has a *negative* value of $\Delta G^\ominus$ (energy is released). A reaction that has a positive value of $\Delta G^\ominus$ (energy must be added) is unfavorable. These predictions agree with our intuition that reactions should go from higher-energy states to lower-energy states, with a net decrease in free energy.

---

① Absolute temperatures (in kelvins) are correctly given without a degree sign, as in the equation 25 ℃ = 298 K. We will often include the degree sign, however, to distinguish absolute temperatures (K) from equilibrium constants (K) as in 25 ℃ = 298°K.

SOLVED PROBLEM 5-1

Calculate the value of $\Delta G^{\ominus}$ for the chlorination of methane.

SOLUTION

$$\Delta G^{\ominus} = -2.303\ RT(\lg K_{eq})$$

K_{eq} for the chlorination is 1.1×10^{19}, and $\lg K_{eq} = 19.04$

At 25 ℃ (about 298 K), the value of RT is

$$RT = [8.314\ \text{J/(mol·K)}](298\ \text{K}) = 2478\ \text{J/mol, or } 2.48\ \text{kJ/mol}$$

Substituting, we have

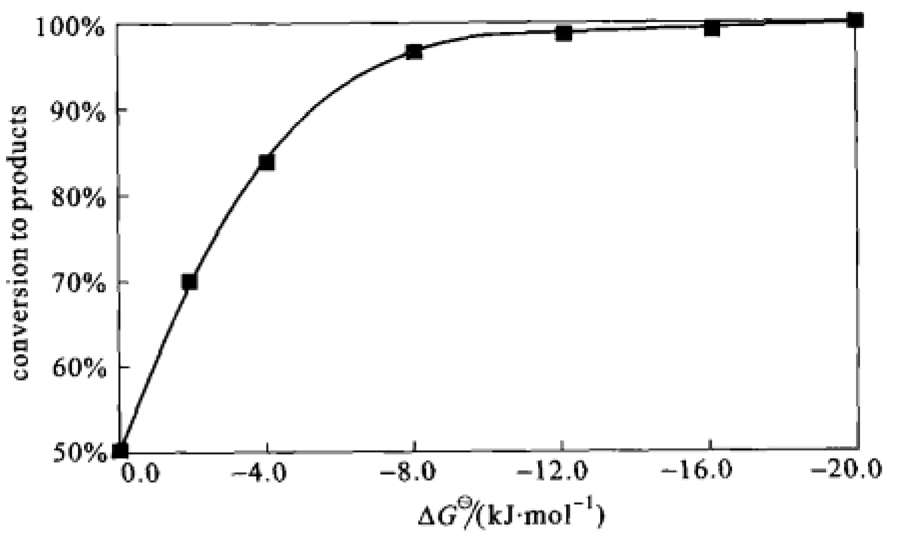
$$\Delta G^{\ominus} = (-2.303)(2.478\ \text{kJ/mol})(19.04) = -108.7\ \text{kJ/mol}$$

This is a large negative value for $\Delta G^{\ominus}$, showing that this chlorination has a large driving force that pushes it toward completion.

In general, a reaction goes nearly to completion (>99%) for values of $\Delta G^{\ominus}$ that are more negative than about -12 kJ/mol. Table 5-1 shows what percentages of the starting materials are converted to products at equilibrium for reactions with various values of $\Delta G^{\ominus}$.

TABLE 5-1 Product Composition as a Function of ΔG at 25 C

$\Delta G^{\ominus}$ / kJ·mol^{-1}	K	conversion to products
+4.0	0.20	17%
+2.0	0.45	31%
0.0	1.0	50%
-2.0	2.2	69%
-4.0	5.0	83%
-8.0	25	96%
-12.0	127	99.2%
-16.0	638	99.8%
-20.0	3 200	99.96%



PROBLEM 5-3

The following reaction has a value of $\Delta G^{\ominus} = -2.1$ kJ/mol.

$$CH_3Br + H_2S \rightleftharpoons CH_3SH + HBr$$

(a) Calculate K_{eq} at room temperature (25 ℃) for this reaction as written.

(b) Starting with a 1 mol/L solution of CH_3Br and H_2S, calculate the final concentrations of all four species at equilibrium.

5-5 Enthalpy and Entropy

Two factors contribute to the change in free energy: the change in **enthalpy** and the change in **entropy**

multiplied by the temperature.

$$\Delta G^{\ominus} = \Delta H^{\ominus} - T\Delta S^{\ominus}$$

$\Delta G^{\ominus}$ = (free energy of products) - (free energy of reactants)

$\Delta H^{\ominus}$ = (enthalpy of products) - (enthalpy of reactants)

$\Delta S^{\ominus}$ = (entropy of products) - (entropy of reactants)

At low temperatures, the enthalpy term ($\Delta H^{\ominus}$) is usually much larger than the entropy term ($-T\Delta S^{\ominus}$), and the entropy term is sometimes ignored.

5-5A Enthalpy

The **change in enthalpy** ($\Delta H^{\ominus}$) is the heat of reaction—the amount of heat evolved or consumed in the course of a reaction, usually given in kilojoules (or kilocalories) per mole. The enthalpy change is a measure of the relative strength of bonding in the products and reactants. Reactions tend to favor products with the lowest enthalpy (those with the strongest bonds).

If weaker bonds are broken and stronger bonds are formed, heat is evolved and the reaction is **exothermic** (negative value of $\Delta H^{\ominus}$). In an exothermic reaction, the enthalpy term makes a favorable negative contribution to $\Delta G^{\ominus}$. If stronger bonds are broken and weaker bonds are formed, then energy is consumed in the reaction, and the reaction is **endothermic** (positive value of $\Delta H^{\ominus}$). In an endothermic reaction, the enthalpy term makes an unfavorable positive contribution to $\Delta G^{\ominus}$.

The value of $\Delta H^{\ominus}$ for the chlorination of methane is about -105.1 kJ/mol. This is a highly exothermic reaction, with the decrease in enthalpy serving as the primary driving force.

5-5B Entropy

Entropy is often described as randomness, or freedom of motion. Reactions tend to favor products with the greatest entropy. Notice the negative sign in the entropy term ($-T\Delta S^{\ominus}$) of the free-energy expression. A positive value of the entropy change ($\Delta S^{\ominus}$), indicating that the products have more freedom of motion than the reactants, makes a favorable (negative) contribution to $\Delta G^{\ominus}$.

In many cases, the enthalpy change ($\Delta H^{\ominus}$) is much larger than the entropy change ($\Delta S^{\ominus}$), and the enthalpy term dominates the equation for $\Delta G^{\ominus}$. Thus, a negative value of $\Delta S^{\ominus}$ does not necessarily mean that the reaction has an unfavorable value of $\Delta G^{\ominus}$. The formation of strong bonds (the change in enthalpy) is usually the most important component in the driving force for a reaction.

In the chlorination of methane, the value of $\Delta S^{\ominus}$ is +12.1 J/(mol·K). The $-T\Delta S^{\ominus}$ term in the free energy is

$$-T\Delta S^{\ominus} = -(298\ \text{K})[12.1\ \text{J/(mol·K)}] = -3\,606\ \text{J/mol}$$
$$\approx -3.61\ \text{kJ/mol}$$

The value of $\Delta G^{\ominus}$ = -108.7 kJ/mol is divided into enthalpy and entropy terms:

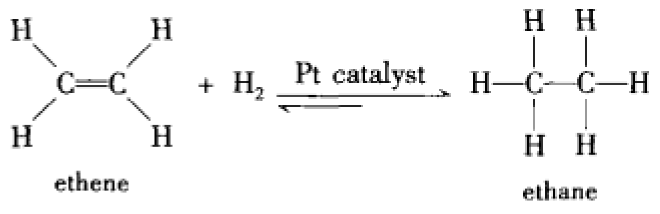
$$\Delta G^{\ominus} = \Delta H^{\ominus} - T\Delta S^{\ominus} = -105.1\ \text{kJ/mol} - 3.61\ \text{kJ/mol}$$
$$= -108.7\ \text{kJ/mol}$$

The enthalpy change is the largest factor in the driving force for chlorination. This is the case in most organic reactions: The entropy term is often small in relation to the enthalpy term. When we discuss chemical reactions involving the breaking and forming of bonds, we can often use the values of the enthalpy changes ($\Delta H^{\ominus}$), under the assumption that $\Delta G^{\ominus} \approx \Delta H^{\ominus}$. We must be cautious in making this approximation, however, because some

reactions have relatively small changes in enthalpy and larger changes in entropy.

PROBLEM 5−4

When ethene is mixed with hydrogen in the presence of a platinum catalyst, hydrogen adds across the double bond to form ethane. At room temperature, the reaction goes to completion. Predict the signs of $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ for this reaction. Explain these signs in terms of bonding and freedom of motion.



5−6 Bond-Dissociation Enthalpies

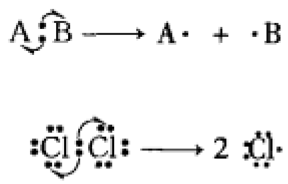
We can put known amounts of methane and chlorine into a bomb calorimeter and use a hot wire to initiate the reaction. The temperature rise in the calorimeter is used to calculate the precise value of the heat of reaction, $\Delta H^{\ominus}$. This measurement shows that 105 kJ of heat is evolved (exothermic) for each mole of methane converted to chloromethane. Thus, $\Delta H^{\ominus}$ for the reaction is negative, and the heat of reaction is given as

$$\Delta H^{\ominus} = -105 \text{ kJ/mol}$$

In many cases, we want to predict whether a particular reaction will be endothermic or exothermic, without actually measuring the heat of reaction. We can calculate an approximate heat of reaction by adding and subtracting the energies involved in the breaking and forming of bonds. To do this calculation, we need to know the energies of the affected bonds.

The **bond-dissociation enthalpy** (**BDE**, also called **bond-dissociation energy**) is the amount of enthalpy required to break a particular bond **homolytically**, that is, in such a way that each bonded atom retains one of the bond's two electrons. In contrast, when a bond is broken **heterolytically**, one of the atoms retains both electrons.

Homolytic cleavage (free radicals result)



$\Delta H^{\ominus}$ = bond-dissociation enthalpy (键解离焓)

$\Delta H^{\ominus}$ = 242 kJ/mol

Heterolytic cleavage (ions result)

($\Delta H^{\ominus}$ varies with solvent)

Homolytic cleavage (**radical cleavage**) forms free radicals, while **heterolytic cleavage** (**ionic cleavage**) forms ions. Enthalpies for heterolytic (ionic) cleavage depend strongly on the solvent's ability to solvate the ions that result. Homolytic cleavage is used to define bond-dissociation enthalpies because the values do not vary so

much with different solvents or with no solvent. Note that a curved arrow is used to show the movement of the electron pair in an ionic cleavage, and curved half-arrows are used to show the separation of individual electrons in a homolytic cleavage.

Energy is released when bonds are formed, and energy is consumed to break bonds. Therefore, bond-dissociation enthalpies are always positive (endothermic). The overall enthalpy change for a reaction is the sum of the dissociation enthalpies of the bonds broken minus the sum of the dissociation enthalpies of the bonds formed.

$$\Delta H^{\ominus} = \sum(\text{BDE of bonds broken}) - \sum(\text{BDE of bonds formed})$$

By studying the heats of reaction for many different reactions, chemists have developed reliable tables of bond-dissociation enthalpies. Table 5-2 gives the bond-dissociation enthalpies for the homolysis of bonds in a variety of molecules.

TABLE 5-2 Bond-Dissociation Enthalpies for Homolytic Cleavages

$$A:B \longrightarrow A\cdot + \cdot B$$

Bond	Bond-Dissociation Enthalpy /(kJ·mol^{-1})
H—X bonds and X—X bonds	
H—H	435
D—D	444
F—F	159
Cl—Cl	242
Br—Br	192
I—I	151
H—F	569
H—Cl	431
H—Br	368
H—I	297
HO—H	498
HO—OH	213
Methyl bonds	
CH_3—H	435
CH_3—F	456
CH_3—Cl	351
CH_3—Br	293
CH_3—I	234
CH_3—OH	381
Bonds to primary carbons	
CH_3CH_2—H	410
CH_3CH_2—F	448
CH_3CH_2—Cl	339
CH_3CH_2—Br	285
CH_3CH_2—I	222
CH_3CH_2—OH	381
$CH_3CH_2CH_2$—H	410
$CH_3CH_2CH_2$—F	448
$CH_3CH_2CH_2$—Cl	339
$CH_3CH_2CH_2$—Br	285
$CH_3CH_2CH_2$—I	222
$CH_3CH_2CH_2$—OH	381
Bonds to secondary carbons	
$(CH_3)_2CH$—H	397
$(CH_3)_2CH$—F	444
$(CH_3)_2CH$—Cl	335
$(CH_3)_2CH$—Br	285
$(CH_3)_2CH$—I	222
$(CH_3)_2CH$—OH	381
Bonds to tertiary carbons	
$(CH_3)_3C$—H	381
$(CH_3)_3C$—F	444
$(CH_3)_3C$—Cl	331
$(CH_3)_3C$—Br	272
$(CH_3)_3C$—I	209
$(CH_3)_3C$—OH	381
Other C—H bonds	
$PhCH_2$—H (benzylic)	356
CH_2═$CHCH_2$—H (allylic)	364
CH_2═CH—H (vinyl)	464
Ph—H (aromatic)	473
C—C bonds	
CH_3—CH_3	368
CH_3CH_2—CH_3	356
CH_3CH_2—CH_2CH_3	343
$(CH_3)_2CH$—CH_3	351
$(CH_3)_3C$—CH_3	339

5-7 Enthalpy Changes in Chlorination

We can use values from Table 5-2 to predict the heat of reaction for the chlorination of methane. This reaction involves the breaking (positive values) of a CH_3—H bond and a Cl—Cl bond, and the formation (negative values) of a CH_3—Cl bond and a H—Cl bond.

Overall reaction

$$CH_3\text{—}H + Cl\text{—}Cl \longrightarrow CH_3\text{—}Cl + H\text{—}Cl$$

Bonds broken	$\Delta H^{\ominus}$ (*per mole*)	*Bonds formed*	$\Delta H^{\ominus}$ (*per mole*)
Cl—Cl	+242 kJ	H—Cl	-431 kJ
CH_3—H	+435 kJ	CH_3—Cl	-351 kJ
Total	**+677 kJ**	**Total**	**-782 kJ**

$$\Delta H^{\ominus} = +677 \text{ kJ/mol} + (-782) \text{ kJ/mol} = -105 \text{ kJ/mol}$$

The bond-dissociation enthalpies also provide the heat of reaction for each individual step:

First propagation step

$$Cl\cdot + CH_4 \longrightarrow \cdot CH_3 + HCl$$

Breaking a CH_3—H bond	+435 kJ/mol
Forming an H—Cl bond	-431 kJ/mol
Step total	+4 kJ/mol

Second propagation step

$$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$

Breaking a Cl—Cl bond	+243 kJ/mol
Forming a CH_3—Cl bond	-352 kJ/mol
Step total	-109 kJ/mol

$$\text{Grand total} = +4 \text{ kJ/mol} + (-109 \text{ kJ/mol}) = -105 \text{ kJ/mol}$$

The sum of the values of $\Delta H^{\ominus}$ for the individual propagation steps gives the overall enthalpy change for the reaction. The initiation step, $Cl_2 \longrightarrow 2\ Cl\cdot$, is not added to give the overall enthalpy change because it is not necessary for each molecule of product formed. The first splitting of a chlorine molecule simply begins the chain reaction, which generates hundreds or thousands of molecules of chloromethane.

PROBLEM 5-5

(a) Propose a mechanism for the free-radical chlorination of ethane,

$$CH_3\text{—}CH_3 + Cl_2 \xrightarrow{h\nu} CH_3\text{—}CH_2Cl + HCl$$

(b) Calculate $\Delta H^{\ominus}$ for each step in this reaction.

(c) Calculate the overall value of $\Delta H^{\ominus}$ for this reaction.

Alternative Mechanism The mechanism we have used is not the only one that might be proposed to explain the reaction of methane with chlorine. We know that the initiating step must be the splitting of a molecule of Cl_2, but

there are other propagation steps that would form the correct products:

(a) $Cl\cdot + CH_3—H \longrightarrow CH_3—Cl + H\cdot$ $\Delta H^{\ominus} = +435\ kJ - 351\ kJ = +84\ kJ$

(b) $H\cdot + Cl—Cl \longrightarrow H—Cl + Cl\cdot$ $\Delta H^{\ominus} = +242\ kJ - 431\ kJ = -189\ kJ$

Total -105 kJ

This alternative mechanism seems plausible, but Step (a) is endothermic by 84 kJ/mol. The previous mechanism provides a lower-energy alternative. When a chlorine atom collides with a methane molecule, it will not react to give methyl chloride and a hydrogen atom ($\Delta H^{\ominus} = +84$ kJ); it will react to give HCl and a methyl radical ($\Delta H^{\ominus} = +4$ kJ), the first propagation step of the correct mechanism.

5-8 Kinetics and the Rate Equation

Kinetics is the study of reaction rates. How fast a reaction goes is just as important as the position of its equilibrium. Just because thermodynamics favors a reaction (negative $\Delta G^{\ominus}$) does not necessarily mean the reaction will actually occur. For example, a mixture of gasoline and oxygen does not react without a spark or a catalyst. Similarly, a mixture of methane and chlorine does not react if it is kept cold and dark.

The **rate of a reaction** is a measure of how fast the products appear and the reactants disappear. We can determine the rate by measuring the increase in the concentrations of the products with time, or the decrease in the concentrations of the reactants with time.

Reaction rates depend on the concentrations of the reactants. The greater the concentrations, the more often the reactants collide and the greater the chance of reaction. A **rate equation** (sometimes called a **rate law**) is the relationship between the concentrations of the reactants and the observed reaction rate. Each reaction has its own rate equation, *determined experimentally* by changing the concentrations of the reactants and measuring the change in the rate. For example, consider the general reaction

$$A + B \longrightarrow C + D$$

The reaction rate is usually proportional to the concentrations of the reactants ([A] and [B]) raised to some powers, a and b. We can use a general rate expression to represent this relationship as

$$\text{rate} = k_r[A]^a[B]^b$$

where k_r is the **rate constant**, and the values of the powers (a and b) must be determined experimentally. We cannot guess or calculate the rate equation from just the stoichiometry of the reaction. The rate equation depends on the mechanism of the reaction and on the rates of the individual steps in the mechanism.

In the general rate equation, the power a is called the **order** of the reaction with respect to reactant A, and b is the order of the reaction with respect to B. The sum of these powers, $(a + b)$, is called the **overall order** of the reaction.

The following reaction has a simple rate equation:

$$CH_3—Br + {}^-OH \xrightarrow{H_2O/\text{acetone}} CH_3—OH + Br^-$$

Experiments show that doubling the concentration of methyl bromide, $[CH_3Br]$, doubles the rate of reaction. Doubling the concentration of hydroxide ion, $[{}^-OH]$, also doubles the rate. Thus, the rate is proportional to both $[CH_3Br]$ and $[{}^-OH]$, so the rate equation has the following form:

$$\text{rate} = k_r[CH_3Br][{}^-OH]$$

This rate equation is *first order* in each of the two reagents because it is proportional to the first power of their

concentrations. The rate equation is *second order overall* because the sum of the powers of the concentrations in the rate equation is 2; that is, (first order) + (first order) = second order overall.

Reactions of the same overall type do not necessarily have the same form of rate equation. For example, the following similar reaction has a different kinetic order:

$$(CH_3)_3C\text{—}Br + {}^-OH \xrightarrow{H_2O\ /acetone} (CH_3)_3C\text{—}OH + Br^-$$

Doubling the concentration of *t*-butyl bromide [$(CH_3)_3C\text{—}Br$] causes the rate to double, but doubling the concentration of hydroxide ion [^-OH] has no effect on the rate of this particular reaction. The rate equation is

$$\text{rate} = k_r[(CH_3)_3C\text{—}Br]$$

This reaction is first order in *t*-butyl bromide, and zeroth order in hydroxide ion (proportional to [^-OH] to the zeroth power). It is first order overall.

The most important fact to remember is that *the rate equation must be determined experimentally*. We cannot predict the form of the rate equation from the stoichiometry of the reaction. We determine the rate equation experimentally, then use that information to propose consistent mechanisms.

PROBLEM 5-6

The reaction of *t*-butyl chloride with methanol

$$\underset{t\text{-butyl chloride}}{(CH_3)_3C\text{—}Cl} + \underset{\text{methanol}}{CH_3\text{—}OH} \longrightarrow \underset{\text{methyl } t\text{-butyl ether}}{(CH_3)_3C\text{—}OCH_3} + HCl$$

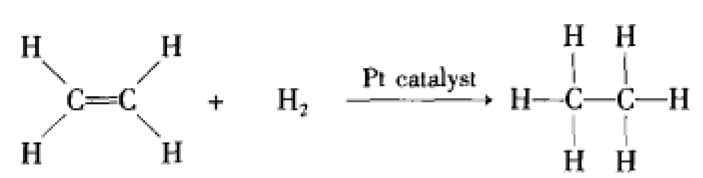
is found to follow the rate equation

$$\text{rate} = k_r[(CH_3)_3C\text{—}Cl]$$

(a) What is the kinetic order with respect to *t*-butyl chloride?
(b) What is the kinetic order with respect to methanol?
(c) What is the kinetic order overall?

PROBLEM 5-7

When a small piece of platinum is added to a mixture of ethene and hydrogen, the following reaction occurs:



ethene hydrogen ethane

Doubling the concentration of hydrogen has no effect on the reaction rate. Doubling the concentration of ethene also has no effect.

(a) What is the kinetic order of this reaction with respect to ethene? With respect to hydrogen? What is the overall order?
(b) Write the unusual rate equation for this reaction.
(c) Explain this strange rate equation, and suggest what one might do to accelerate the reaction.

5-9 Activation Energy and the Temperature Dependence of Rates

Each reaction has its own characteristic rate constant, k_r. Its value depends on the conditions of the reaction,

especially the temperature. This temperature dependence is expressed by the *Arrhenius equation*,

$$k_r = A\mathrm{e}^{-E_a/(RT)}$$

where

A = a constant (the "frequency factor")

E_a = activation energy

R = the gas constant. 8.314 J/(mol·K)

T = the absolute temperature

The **activation energy**, E_a, is the minimum kinetic energy the molecules must have to overcome the repulsions between their electron clouds when they collide. The exponential term $\mathrm{e}^{-E_a/(RT)}$ corresponds to the fraction of collisions in which the particles have the minimum energy E_a needed to react. We can calculate E_a for a reaction by measuring how k_r varies with temperature, and substituting into the Arrhenius equation.

The *frequency factor A* accounts for the frequency of collisions and the fraction of collisions with the proper orientation for the reaction to occur. In most cases, only a small fraction of collisions occur between molecules with enough speed and with just the right orientation for reaction to occur. Far more collisions occur without enough kinetic energy or without the proper orientation, and the molecules simply bounce off each other.

The Arrhenius equation implies that the rate of a reaction depends on the fraction of molecules with kinetic energy of at least E_a. Figure 5-2 shows how the distribution of kinetic energies in a sample of a gas depends on the temperature. The one curved line shows the molecular energy distribution at room temperature, and the dashed lines show the energy needed to overcome barriers of 4 kJ/mol, 40 kJ/mol, and 80 kJ. The area under the curve to the right of each barrier corresponds to the number of molecules with enough energy to overcome that barrier. The another curve shows how the energy distribution is shifted at 100 ℃. At 100 ℃, many more molecules have the energy needed to overcome the energy barriers especially the 80 kJ/mol barrier. For smaller temperature changes, chemists often use an approximation: For reactions with typical activation energies of about 40 to 60 kJ/mol, the reaction rate approximately doubles when the temperature is raised by 10 ℃, as from 27 ℃ (near room temperature) to 37 ℃ (body temperature).

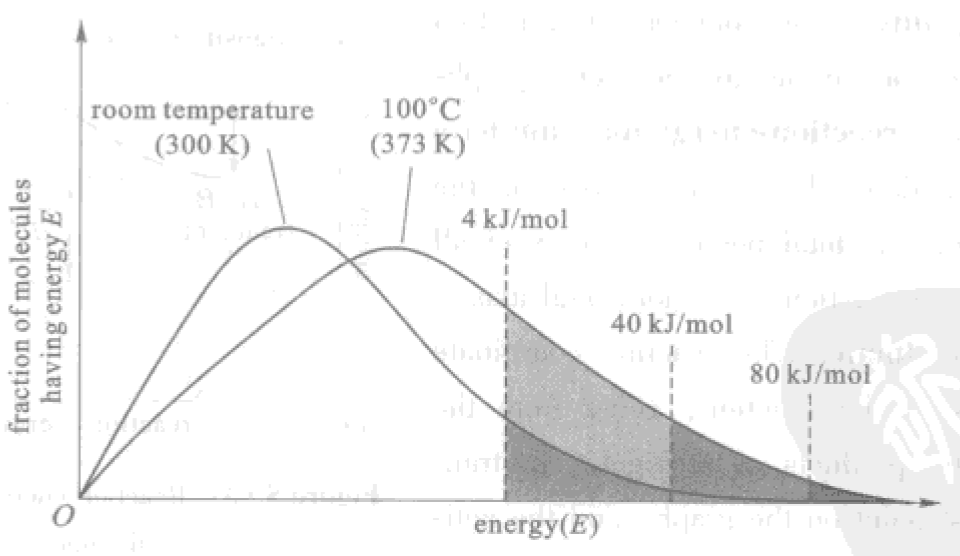


Figure 5-2 The dependence of kinetic energies on temperature. This graph shows how the number of molecules with a given activation energy decreases as the activation energy increases. At a higher temperature, more collisions have the needed energy.

Because the relative rate constant, k_{rel}, increases quickly when the temperature is raised, it might seem that raising the temperature would always be a good way to save time by making reactions go faster. The problem with raising the temperature is that *all* reactions are accelerated, including all the unwanted side reactions. We try to

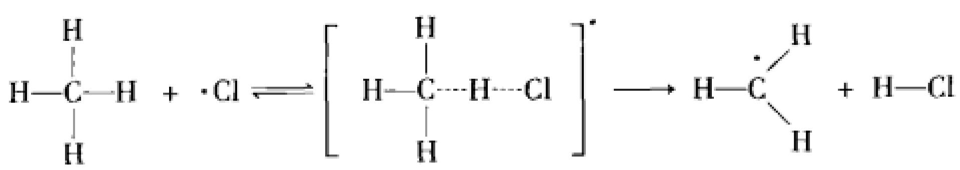
find a temperature that allows the desired reaction to go at a reasonable rate without producing unacceptable rates of side reactions.

5-10 Transition States

The activation energy E_a represents the energy difference between the reactants and the **transition state**, the highest-energy state in a molecular collision that leads to reaction. In effect, the activation energy is the barrier that must be overcome for the reaction to take place. The value of E_a is always positive, and its magnitude depends on the relative energy of the transition state. The term *transition state* implies that this configuration is the transition between the reactants and products, and the molecules can either go on to products or return to reactants.

Unlike the reactants or products, a transition state is unstable and cannot be isolated. It is not an intermediate, because an **intermediate** is a species that exists for some finite length of time, even if it is very short. An intermediate has at least some stability, but the transition state is a transient on the path from one intermediate to another. The transition state is often symbolized by a superscript double dagger ($\ddagger$), and the changes in variables such as free energy, enthalpy, and entropy involved in achieving the transition state are symbolized $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$. $\Delta G^{\ddagger}$ is similar to E_a, and the symbol $\Delta G^{\ddagger}$ is often used in speaking of the activation energy.

Transition states have high energies because bonds must begin to break before other bonds can form. The following equation shows the reaction of a chlorine radical with methane. The transition state shows the C—H bond partially broken and the H—Cl bond partially formed. Transition states are often enclosed by brackets to emphasize their transient nature.



transition state (过渡态)

Reaction-Energy Diagrams The concepts of transition state and activation energy are easier to understand graphically. Figure 5-3 shows a **reaction-energy diagram** for a one-step exothermic reaction. The vertical axis of the energy diagram represents the total potential energy of all the species involved in the reaction. The horizontal axis is called the **reaction coordinate**. The reaction coordinate symbolizes the progress of the reaction, going from the reactants on the left to the products on the right. The transition state is the highest point on the graph, and the activation energy is the energy difference between the reactants and the transition state. The heat of reaction ($\Delta H^{\ominus}$) is the difference in energy between the reactants and the products.

If a **catalyst** were added to the reaction in Figure 5-3, it would create a transition state of lower energy, thereby lowering the activation energy. Addition of a cata-

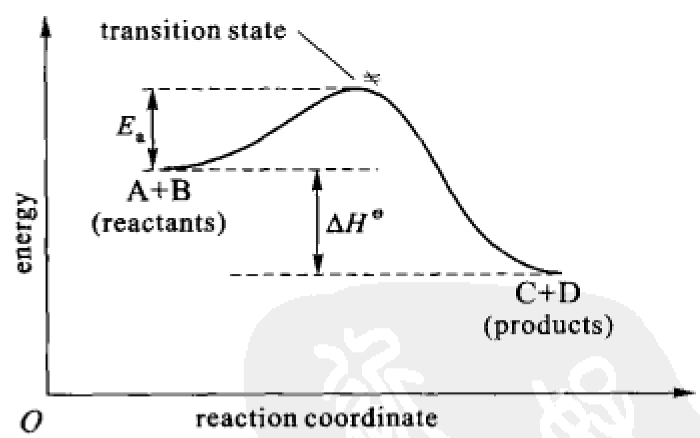


Figure 5-3 Reaction-energy diagram for a one-step exothermic reaction. The reactants are toward the left, and the products are toward the right. The vertical axis represents the potential energy. The transition state is the highest point on the graph, and the activation energy is the energy difference between the reactants and the transition state.

lyst would not change the energies of the reactants and products, however, so the heat of reaction and the equilibrium constant would be unaffected.

PROBLEM 5-8

(a) Draw a reaction-energy diagram for the following reaction:

$$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$

The activation energy is 4 kJ/mol, and the overall $\Delta H^\ominus$ for the reaction is -109 kJ/mol.

(b) Give the equation for the reverse reaction.

(c) What is the activation energy for the reverse reaction?

5-11 Rates of Multistep Reactions

Many reactions proceed by mechanisms involving several steps and several intermediates. As we saw in Section 5-7, for example, the reaction of methane with chlorine goes through two propagation steps. The propagation steps are shown here, along with their heats of reaction and their activation energies. Just the propagation steps are shown because the rate of the initiation step is controlled by the amount of light or heat available to split chlorine molecules.

Step	$\Delta H^\ominus$ (per mole)	E_a (per mole)
$CH_4 + Cl\cdot \longrightarrow \cdot CH_3 + HCl$	+4 kJ	17 kJ
$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$	−109 kJ	4 kJ

In this reaction, $Cl\cdot$ and $CH_3\cdot$ are *reactive intermediates*. Unlike transition states, reactive intermediates are stable as long as they do not collide with other atoms or molecules. As free radicals, however, $Cl\cdot$ and $CH_3\cdot$ are quite reactive toward other molecules. Figure 5-4 shows a single reaction-energy profile that includes both propagation steps of the chlorination. The energy maxima (high points) are the unstable transition states, and the energy minima (low points) are the intermediates. This complete energy profile provides most of the important information about the energetics of the reaction.

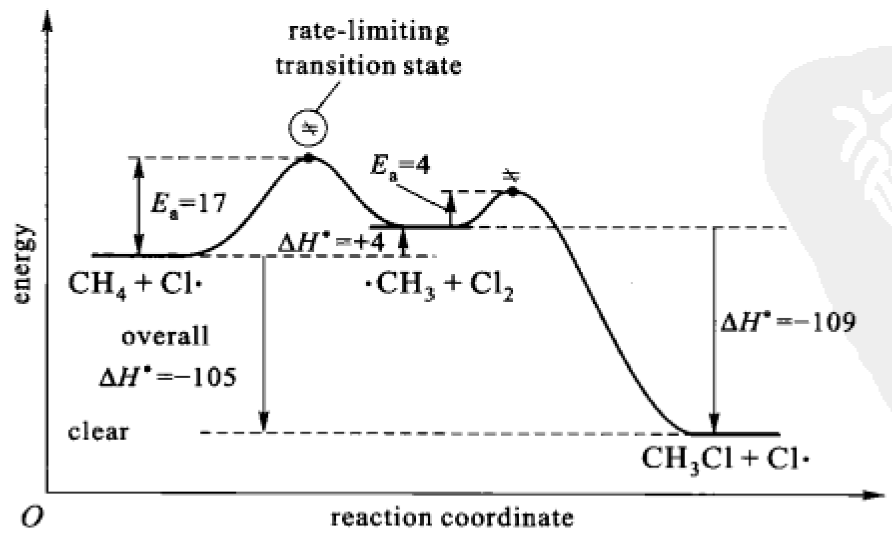


Figure 5-4 Combined reaction-energy diagram for the chlorination of methane. The energy maxima are transition states, and the energy minima are intermediates. (Units are kJ/mol.)

The Rate-Limiting Step In a multistep reaction, each step has its own characteristic rate. There can be only one overall reaction rate, however, and it is controlled by the **rate-limiting step** (also called the **rate-determining step**). In general, the *highest-energy* step of a multistep reaction is the "bottleneck," and it determines the overall rate. How can we tell which step is rate limiting? If we have the reaction-energy diagram, it is simple: The highest point in the energy diagram is the transition state with the highest energy—the transition state for the rate-limiting step.

The highest point in the energy diagram of the chlorination of methane (Figure 5-4) is the transition state for the reaction of methane with a chlorine radical. This step must be rate limiting. If we calculate a rate for this slow step, it will be the rate for the overall reaction. The second, faster step will consume the products of the slow step as fast as they are formed.

5-12 Temperature Dependence of Halogenation

We now apply what we know about rates to the reaction of methane with halogens. The rate-limiting step for chlorination is the endothermic reaction of the chlorine atom with methane to form a methyl radical and a molecule of HCl.

Rate-limiting step

$$CH_4 + Cl\cdot \longrightarrow \cdot CH_3 + HCl$$

The activation energy for this step is 17 kJ/mol. At room temperature, the value of $e^{-E_a/(RT)}$ is $1\,300 \times 10^{-6}$. This value represents a rate that is fast but controllable.

In a free-radical chain reaction, every propagation step must occur quickly, or the free radicals will undergo unproductive collisions and become involved in termination steps. We can predict how quickly the various halogen atoms react with methane given relative rates based on the measured activation energies of the slowest steps:

Reaction	E_a (per mole)	Relative Rate ($e^{-E_a/(RT)} \times 10^6$)	
		27 ℃ (300 K)	227 ℃ (500 K)
$F\cdot + CH_4 \longrightarrow HF + \cdot CH_3$	5 kJ	140 000	300 000
$Cl\cdot + CH_4 \longrightarrow HCl + \cdot CH_3$	17 kJ	1 300	18 000
$Br\cdot + CH_4 \longrightarrow HBr + \cdot CH_3$	75 kJ	9×10^{-8}	0.015
$I\cdot + CH_4 \longrightarrow HI + \cdot CH_3$	140 kJ	2×10^{-19}	2×10^{-9}

These relative rates suggest how easily and quickly methane reacts with the different halogen radicals. The reaction with fluorine should be difficult to control because its rate is very high. Chlorine should react moderately at room temperature, but it may become difficult to control if the temperature rises much (the rate at 500 K is rather high). The reaction with bromine is very slow, but heating might give an observable rate. Iodination is probably out of the question because its rate is exceedingly slow, even at 500 K.

Laboratory halogenations show that our predictions are right. In fact, fluorine reacts explosively with methane, and chlorine reacts at a moderate rate. A mixture of bromine and methane must be heated to react, and iodine does not react at all.

PROBLEM 5-9

The bromination of methane proceeds through the following step:

	$\Delta H^{\ominus}$ (per mole)	E_a (per mole)
$Br_2 \xrightarrow{h\nu} 2\ Br\cdot$	+192 kJ	192 kJ
$CH_4 + Br\cdot \longrightarrow \cdot CH_3 + HBr$	67 kJ	75 kJ
$\cdot CH_3 + Br_2 \longrightarrow CH_3Br + Br\cdot$	−101 kJ	4 kJ

(a) Draw a complete reaction-energy diagram for this reaction.
(b) Label the rate-limiting step.
(c) Draw the structure of each transition state.
(d) Compute the overall value of $\Delta H^{\ominus}$ for the bromination.

5-13 Selectivity in Halogenation

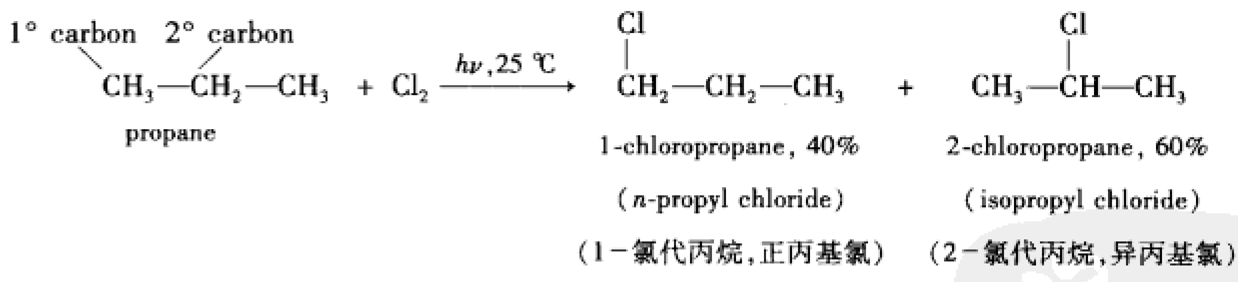
Up to now, we have limited our discussions to the halogenation of methane. Beginning our study with such a simple compound allowed us to concentrate on the thermodynamics and kinetics of the reaction. Now we consider halogenation of the "higher" alkanes, meaning those of higher molecular weight.

5-13A Chlorination of Propane: Product Ratios

Halogenation is a substitution, where a halogen atom replaces a hydrogen.

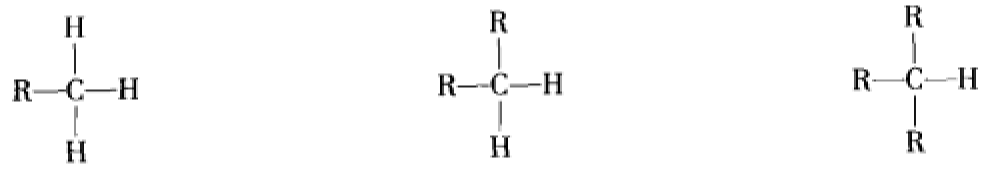
$$R{-}H + X_2 \longrightarrow R{-}X + H{-}X$$

In methane, all four hydrogen atoms are identical, and it does not matter which hydrogen is replaced. In the higher alkanes, replacement of different hydrogen atoms leads to different products. In the chlorination of propane, for example, two monochlorinated (just one chlorine atom) products are possible. One has the chlorine atom on a primary carbon atom, and the other has the chlorine atom on the secondary carbon atom.



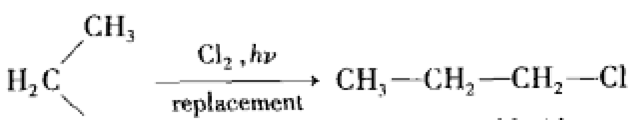
The product ratio shows that replacement of hydrogen atoms by chlorine is not random. Propane has six primary hydrogens (hydrogens bonded to primary carbons) and only two secondary hydrogens (bonded to the secondary carbon), yet the major product results from substitution of a secondary hydrogen. We can calculate how reactive each kind of hydrogen is by dividing the amount of product observed by the number of hydrogens that can be replaced to give that product.

Figure 5-5 shows the definition of primary, secondary, and tertiary hydrogens and the calculation of their relative reactivity. Replacing either of the two secondary hydrogens accounts for 60% of the product, and replacing any of the six primary hydrogens accounts for 40% of the product. We calculate that each secondary hydrogen is 4.5 times as reactive as each primary hydrogen. To explain this preference for reaction at the secondary position, we must look carefully at the reaction mechanism (Figure 5-6).



primary (1°) hydrogens (伯氢) | secondary (2°) hydrogens (仲氢) | tertiary (3°) hydrogen (叔氢)

Six primary (1°) hydrogens *relative reactivity*



primary chloride

$$\frac{40\%}{6\ \text{hydrogens}} = 6.67\%\ \text{per H}$$

Two secondary (2°) hydrogens

secondary chloride

$$\frac{60\%}{2\ \text{hydrogens}} = 30.0\%\ \text{per H}$$

The 2° hydrogens are $\frac{30.0}{6.67} = 4.5$ times as reactive as the 1° hydrogens.

Figure 5−5 Definitions of primary, secondary, and tertiary hydrogens. There are six primary hydrogens in propane and only two secondary hydrogens, yet the major product results from replacement of a secondary hydrogen.

Initiation: Splitting of the chlorine molecule

$$Cl_2 + h\nu \longrightarrow 2\ Cl\cdot$$

First propagation step: Abstraction (removal) of a primary or secondary hydrogen

$$CH_3—CH_2—CH_3 + Cl\cdot \longrightarrow \cdot CH_2—CH_2—CH_3 \text{ or } CH_3—\dot{C}H—CH_3 + HCl$$

primary radical (伯碳自由基) | secondary radical (仲碳自由基)

Second propagation step: Reaction with chlorine to form the alkyl chloride

$$\cdot CH_2—CH_2—CH_3 + Cl_2 \longrightarrow Cl—CH_2—CH_2—CH_3 + Cl\cdot$$

primary radical | primary chloride (1-chloropropane)

$$\text{or}\quad CH_3—\dot{C}H—CH_3 + Cl_2 \longrightarrow CH_3—CH(Cl)—CH_3 + Cl\cdot$$

secondary radical | secondary chloride (2-chloropropane)

Figure 5−6 The mechanism for free-radical chlorination of propane. The first propagation step forms either a primary radical or a secondary radical. This radical determines whether the final product will be the primary chloride or the secondary chloride.

When a chlorine atom reacts with propane, abstraction of a hydrogen atom can give either a primary radical or a secondary radical. The structure of the radical formed in this step determines the structure of the observed

product, either 1-chloropropane of 2-chloropropane. The product ratio shows that the secondary radical is formed preferentially. This preference for reaction at the secondary position results from the greater stability of the secondary free radical and the transition state leading to it.

PROBLEM 5-10

What would be the product ratio in the chlorination of propane if all the hydrogens were abstracted at equal rates?

5-13B Free-Radical Stabilities

Figure 5-7 shows the energy required (the bond-dissociation enthalpy) to form a free radical by breaking a bond between a hydrogen atom and a carbon atom. This energy is greatest for a methyl carbon, and it decreases for a primary carbon, a secondary carbon, and a tertiary carbon. The more highly substituted the carbon atom, the less energy is required to form the free radical.

From the information in Figure 5-7, we conclude that free radicals are more stable if they are more highly substituted. The following free radicals are listed in decreasing order of stability.

Formation of a methyl radical — *Bond-dissociation enthalpy*

$$CH_4 \longrightarrow H\cdot + \cdot CH_3 \qquad \Delta H^{\ominus} = 435\ \text{kJ/mol}$$

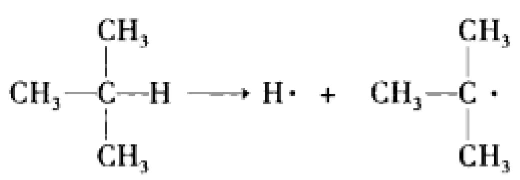
Formation of a primary (1°) radical

$$CH_3{-}CH_2{-}CH_3 \longrightarrow H\cdot + CH_3{-}CH_2{-}\dot{C}H_2 \qquad \Delta H^{\ominus} = 410\ \text{kJ/mol}$$

Formation of a secondary (2°) radical

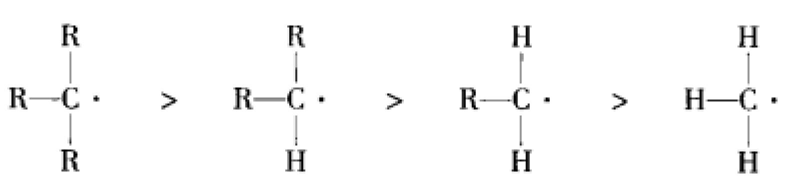
$$CH_3{-}CH_2{-}CH_3 \longrightarrow H\cdot + CH_3{-}\dot{C}H{-}CH_3 \qquad \Delta H^{\ominus} = 397\ \text{kJ/mol}$$

Formation of a tertiary (3°) radical



$\Delta H^{\ominus} = 381\ \text{kJ/mol}$

Figure 5-7 Enthalpy required to form a free radical. Bond-dissociation enthalpies show that more highly substituted free radicals are more stable than less highly substituted ones.



3°	>	2°	>	1°	>	Me·
tertiary	>	secondary	>	primary	>	methyl
(叔)		(仲)		(伯)		(甲基)

In the chlorination of propane, the secondary hydrogen atom is abstracted more often because the secondary radical and the transition state leading to it are lower in energy than the primary radical and its transition state. Using the bond-dissociation enthalpies in Table 5−2, we can calculate $\Delta H^{\ominus}$ for each of the possible reaction steps. Abstraction of the secondary hydrogen is 13 kJ/mol more exothermic than abstraction of the primary hydrogen.

A reaction-energy diagram for this rate-limiting first propagation step appears in Figure 5−8. The activation energy to form the secondary radical is slightly lower, so the secondary radical is formed faster than the primary radical.

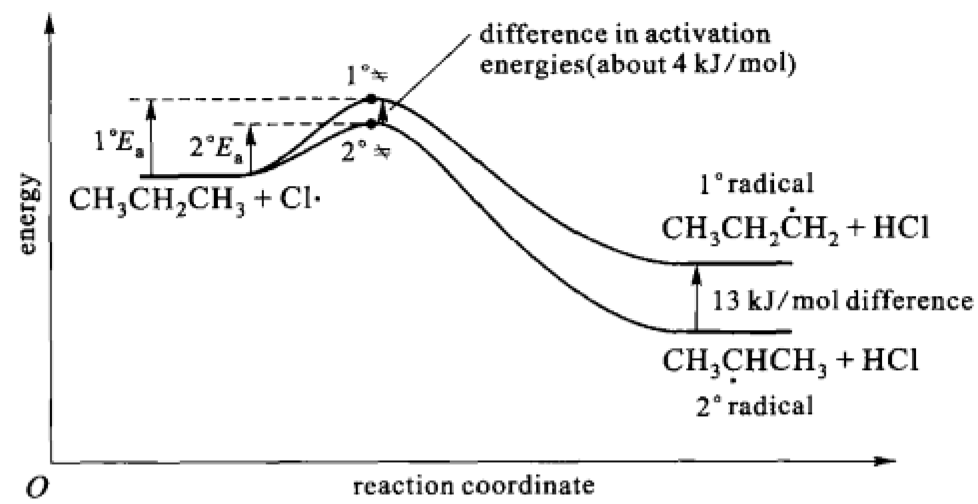


Figure 5−8 Reaction-energy diagram for the first propagation step in the chlorination of propane. Formation of the secondary radical has a lower activation energy than does formation of the primary radical.

PROBLEM 5−11

Tertiary hydrogen atoms react with Cl· about 5.5 times as fast as primary ones. Predict the product rations for chlorination of isobutane.

PROBLEM 5−12

(a) When *n*-heptane burns in a gasoline engine, the combustion process takes place too quickly. The explosive detonation makes a noise called *knocking*. When 2,2,4-trimethylpentane (isooctane) is burned, combustion takes place in a slower, more controlled manner. Combustion is a free-radical chain reaction, and its rate depends on the reactivity of the free-radical intermediates. Explain why isooctane has less tendency to knock than does *n*-heptane.

(b) Alkoxy radicals (R—O·) are generally more stable than alkyl (R·) radicals. Write an equation showing an alkyl free radical (from burning gasoline) abstracting a hydrogen atom from *t*-butyl alcohol, $(CH_3)_3COH$. Explain why *t*-butyl alcohol works as an antiknock additive for gasoline.

5−13C Bromination of Propane

Figure 5−9 shows the free-radical reaction of propane with bromine. Notice that this reaction is both heated to 125 ℃ and irradiated with light to achieve a moderate rate. The secondary bromide (2-bromopropane) is favored by a 97∶3 product ratio. From this product ratio, we calculate that the two secondary hydrogens are each 97 times as reactive as one of the primary hydrogens.

$$CH_3—CH_2—CH_3 + Br_2 \xrightarrow{h\nu, 125\ ℃} CH_3—CH_2—\underset{}{\overset{Br}{\overset{|}{C}}}H_2 + CH_3—\overset{Br}{\overset{|}{C}}H—CH_3 + HBr$$

primary bromide, 3% secondary bromide, 97%

Relative reactivity

six primary hydrogens $\frac{3\%}{6} = 0.5\%$ per H

two secondary hydrogens $\frac{97\%}{2} = 48.5\%$ per H

The 2° hydrogens are $\frac{48.5}{0.5} = 97$ times as reactive as the 1° hydrogens.

Figure 5-9 The free-radical reaction of propane with bromine. This 97 ∶ 3 ratio of products shows that bromine abstracts a secondary hydrogen 97 times as rapidly as a primary hydrogen. Bromination (reactivity ratio 97 ∶ 1) is much more selective than chlorination (reactivity ratio 4.5∶1).

The 97 ∶ 1 reactivity ratio for bromination is much larger than the 4.5 ∶ 1 ratio for chlorination. We say that bromination is more *selective* than chlorination because the major reaction is favored by a larger amount. To explain this enhanced selectivity, we must consider the transition states and activation energies for the rate-limiting step.

As with chlorination, the rate-limiting step in bromination is the first propagation step: abstraction of a hydrogen atom by a bromine radical. The energetics of the two possible hydrogen abstractions are shown below. Compare these numbers with the energetics of the first propagation step of chlorination. The bond dissociation enthalpies are taken from Table 5-2.

1°H: $CH_3—CH_2—CH_3 + Br\cdot \longrightarrow CH_3—CH_2—CH_2\cdot + H—Br$

Energy required to break the $CH_3CH_2CH_2$–H bond	+410 kJ/mol
Energy released in forming the H–Br bond	−368 kJ/mol
Total energy for reaction at the primary position:	+42 kJ/mol

2°H: $CH_3—\overset{CH_3}{\overset{|}{C}}H_2 + Br\cdot \longrightarrow CH_3—\overset{CH_3}{\overset{|}{C}}H\cdot + H—Br$

Energy required to break the $CH_3—\overset{CH_3}{\overset{|}{C}}H$–H bond	+397 kJ/mol
Energy released in forming the H–Br bond	−368 kJ/mol
Total energy for reaction at the secondary position:	+29 kJ/mol

The energy differences between chlorination and bromination result from the difference in the bond-dissociation enthalpies of H—Cl (431 kJ/mol) and H—Br (368 kJ/mol). The HBr bond is weaker, and abstraction of a hydrogen atom by Br· is endothermic. This endothermic step explains why bromination is much slower than chlorination, but it still does not explain the enhanced selectivity observed with bromination.

Consider the reaction-energy diagram for the first propagation step in the bromination of propane (Figure 5-10). Although the difference in values of $\Delta H^{\ominus}$ between abstraction of a primary hydrogen and a secondary hydrogen is still 13 kJ/mol, the energy diagram for bromination shows a much larger difference in activation energies for abstraction of the primary and secondary hydrogens than we saw for chlorination (Figure 5-8).

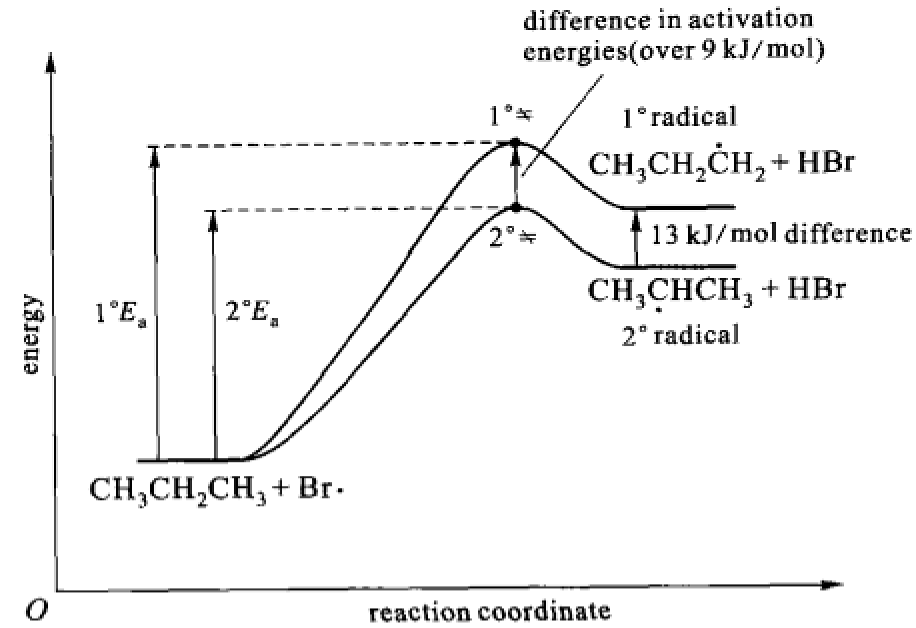
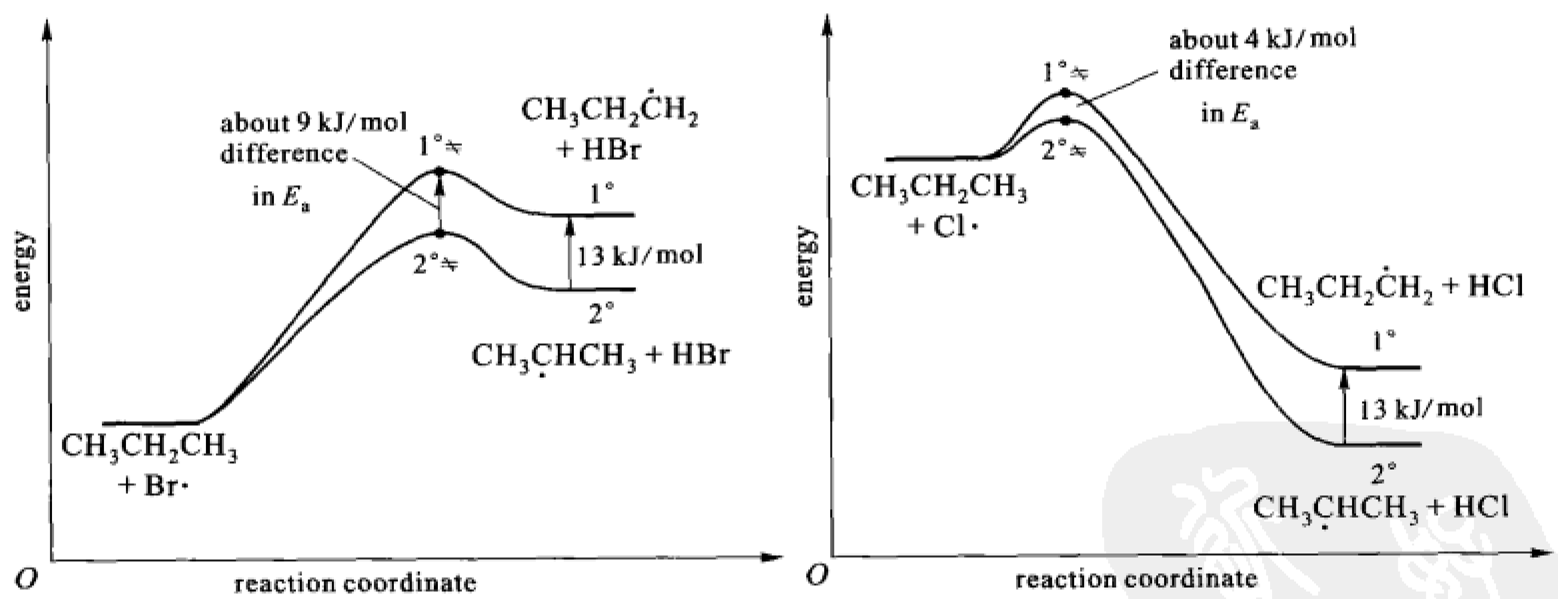


Figure 5−10 Reaction-energy diagram for the first propagation step in the bromination of propane. The energy difference in the transition states is nearly as large as the energy difference in the products.

5−14 The Hammond Postulate

Figure 5−11 summarizes the energy diagrams for the first propagation steps in the bromination and chlorination of propane. Together, these energy diagrams explain the enhanced selectivity observed in bromination.



(a) BROMINATION
endothermic
TS close to products
large difference in E_a

(b) CHLORINATION
exothermic
TS close to reactants
small difference in E_a

Figure 5−11 The energy diagrams for bromination and chlorination of propane.

(**a**) In the endothermic bromination, the transition states are closer to the products (the radicals) in energy and in structure. The difference in the 1° and 2° activation energies is about 9 kJ/mol, nearly the entire energy difference of the radicals.

(**b**) In the exothermic chlorination, the transition states are closer to the reactants in energy and in structure. The difference in activation energies for chlorination is about 4 kJ/mol, only a third of the energy difference of the radicals.

Two important differences are apparent in the reaction-energy diagrams for the first propagation steps of chlorination and bromination:

1. The first propagation step is endothermic for bromination but exothermic for chlorination.

2. The transition states forming the 1° and 2° radicals for the endothermic bromination have a larger energy difference than those for the exothermic chlorination, even though the energy difference of the products is the same (13 kJ/mol) in both reactions.

In general, we will find that these differences are related:

In an endothermic reaction, the transition state is closer to the products in energy and in structure.

In an exothermic reaction, the transition state is closer to the reactants in energy and in structure.

Figure 5-12 compares the transition states for bromination and chlorination. In the product-like transition state for bromination, the C—H bond is nearly broken and the carbon atom has a great deal of radical character. The energy of this transition state reflects most of the energy difference of the radical products. In the reactant-like transition state for chlorination, the C—H bond is just beginning to break, and the carbon atom has little radical character. This transition state reflects only a small part (about a third) of the energy difference of the radical products. Therefore, chlorination is less selective.

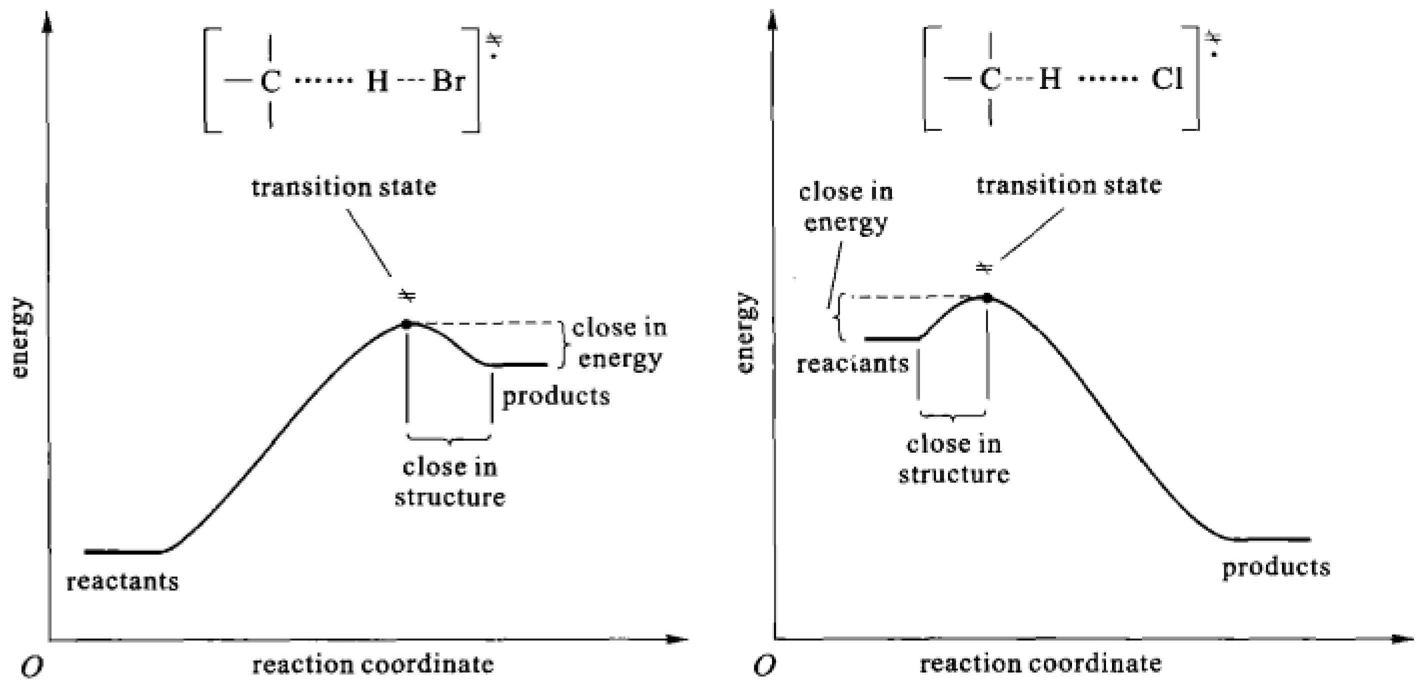


Figure 5-12 Comparison of transition states for bromination and chlorination. In the endothermic bromination, the transition state resembles the products (the free radical and HBr). In the exothermic chlorination, the free radical has just begun to form in the transition state, so the transition state resembles the reactants.

These reactions are examples of a more general principle, called the **Hammond postulate**.

HAMMOND POSTULATE: Related species that are closer in energy are also closer in structure.

The structure of a transition state resembles the structure of the closest stable species.

This general rule tells us something about the transition states in endothermic and exothermic reactions. The transition state is always the point of highest energy on the energy diagram. Its structure resembles either the reactants or the products, whichever ones are higher in energy. In an endothermic reaction, the products are higher in energy, and the transition state is product-like. In an exothermic reaction, the reactants are higher in energy, and the transition state is reactant-like. Thus, the Hammond postulate helps us understand why exothermic

processes tend to be less selective than similar endothermic processes.

PROBLEM 5-13

(a) Compute the heats of reaction for abstraction of a primary hydrogen and a secondary hydrogen from propane by a fluorine radical.

$$CH_3—CH_2—CH_3 + F\cdot \longrightarrow CH_3—CH_2—\dot{C}H_2 + HF$$

$$CH_3—CH_2—CH_3 + F\cdot \longrightarrow CH_3—\dot{C}H—CH_3 + HF$$

(b) How selective do you expect free-radical fluorination to be?

(c) What product distribution would you expect to obtain from the free-radical fluorination of propane?

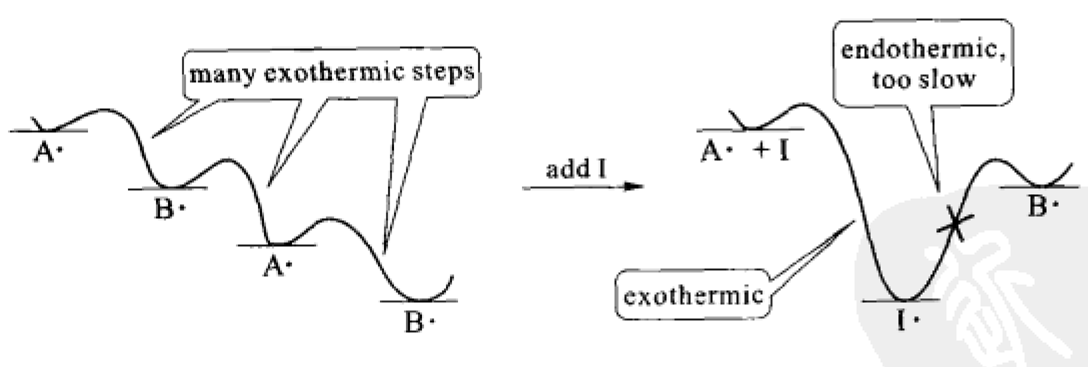
PROBLEM 5-14

2,3-Dimethylbutane reacts with bromine in the presence of light to give a good yield of a monobrominated product. Further reaction gives a dibrominated product. Predict the structures of these products, and propose a mechanism for the formation of the monobrominated product.

5-15 Radical Inhibitors

We often want to prevent or retard free-radical reactions. For example, oxygen in the air oxidizes and spoils foods, solvents, and other compounds mostly by free-radical chain reactions. Chemical intermediates may decompose or polymerize by free-radical chain reactions. Even the cells in living systems are damaged by radical reactions, which can lead to aging, cancerous mutations, or cell death.

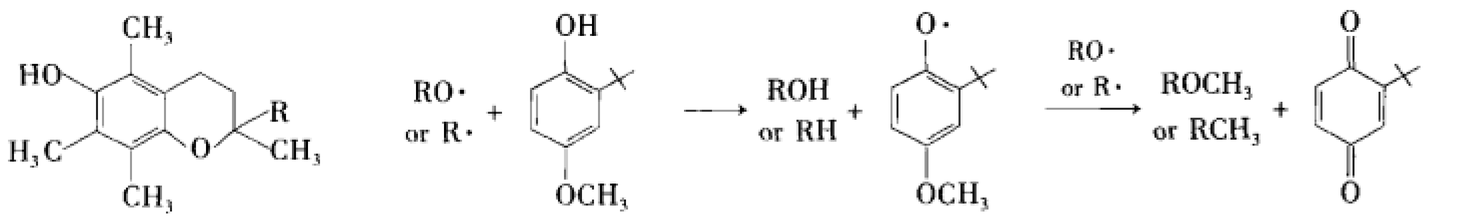
Radical inhibitors are often added to foods and chemicals to retard spoilage by radical chain reactions. Chain reactions depend on the individual steps being fast, so that each initiation step results in many molecules reacting, as in the reaction-energy diagram at the left of the following figure. (Only the radicals are shown.)



chain reaction with inhibitor I

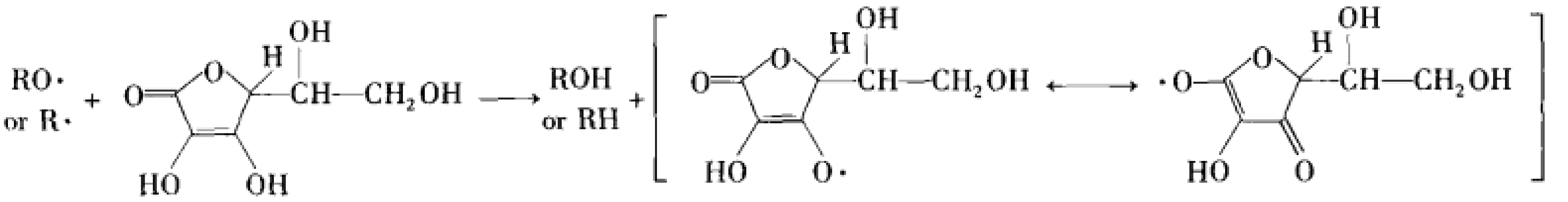
The diagram at right in the figure shows how an inhibitor (I) can stop the chain by reacting with a radical intermediate in a fast, highly exothermic step to form an intermediate that is relatively stable. The next step in the chain becomes endothermic and very slow.

"Butylated hydroxyanisole" (BHA) is often added to foods as an antioxidant. It stops oxidation by reacting with radical intermediates to form a relatively stable free-radical intermediate (BHA radical). The BHA radical can react with a second free radical to form an even more stable quinone with all its electrons paired.



vitamin E (R = alkyl chain) BHA BHA radical a quinone(醌)

Radical inhibitors also help to protect the cells of living systems. Like BHA, vitamin E is a *phenol*, and it is thought to react with radicals by losing the OH hydrogen atom as just shown for BHA. Ascorbic acid (vitamin C) is also thought to protect cells from free radicals, possibly by the following mechanism:



ascorbic acid (抗坏血酸) (vitamin C) stabilized free radical

PROBLEM 5-15

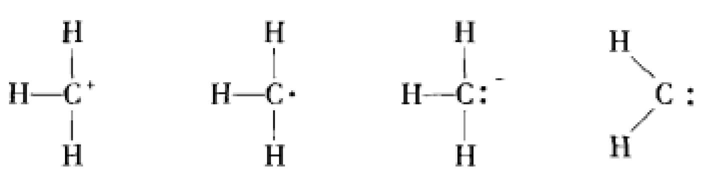
Draw resonance forms to show how the BHA radical is stabilized by delocalization of the radical electron over other atoms in the molecule.

5-16 Reactive Intermediates

The free radicals we have studied are one class of reactive intermediates. **Reactive intermediates** are short-lived species that are never present in high concentrations because they react as quickly as they are formed. In most cases, reactive intermediates are fragments of molecules (like free radicals), often having atoms with unusual numbers of bonds. Some of the common reactive intermediates contain carbon atoms with only two or three bonds, compared with carbon's four bonds in its stable compounds. Such species react quickly with a variety of compounds to give more stable products with tetravalent carbon atoms.

Although reactive intermediates are not stable compounds, they are important to our study of organic chemistry. Most reaction mechanisms involve reactive intermediates. If you are to understand these mechanisms and propose mechanisms of your own, you need to know how reactive intermediates are formed and how they are likely to react. In this chapter, we consider their structure and stability, and in later chapters, we see how they are formed and ways they react to give stable compounds.

Species with trivalent (three-bonded) carbon are classified according to their charge, which depends on the number of nonbonding electrons. The *carbocations* have no nonbonding electrons and are positively charged. The *radicals* have one nonbonding electron and are neutral. The *carbanions* have a pair of nonbonding electrons and are negatively charged.



carbocation (碳正离子) radical (自由基) carbanion (碳负离子) carbene (卡宾)

The most common intermediates with a divalent (two-bonded) carbon atom are the *carbenes*. A carbene has two nonbonding electrons on the divalent carbon atom, making it uncharged.

5–16A Carbocations

A **carbocation** (also called a **carbonium ion** or a **carbenium ion**) is a species that contains a carbon atom bearing a positive charge. The positively charged carbon atom is bonded to three other atoms, and it has no nonbonding electrons, so it has only six electrons in its valence shell. It is sp^2 hybridized, with a planar structure and bond angles of about 120°. For example, the methyl cation (CH_3^+) is planar, with bond angles of exactly 120°. The unhybridized p orbital is vacant and lies perpendicular to the plane of the C—H bonds (Figure 5–13). The structure of CH_3^+ is similar to the structure of BH_3, discussed in Chapter 2.

With only six electrons in the positive carbon's valence shell, a carbocation is a powerful electrophile (Lewis acid), and it may react with any nucleophile it encounters. Carbocations are proposed as intermediates in many organic reactions, some of which we will encounter in Chapter 7.

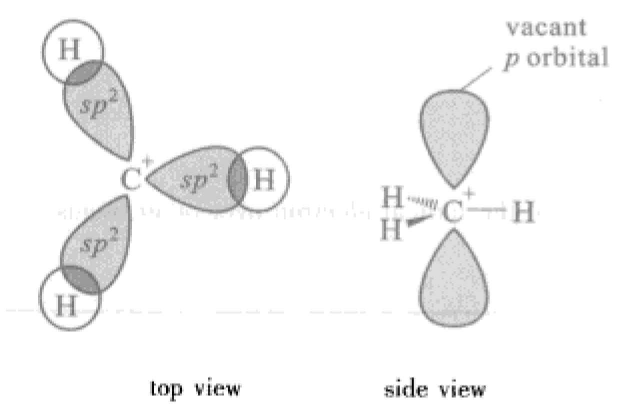


Figure 5–13 Orbital diagram of the methyl cation. The methyl cation is similar to BH_3. The carbon atom is σ bonded to three hydrogen atoms by overlap of its sp^2 hybrid orbitals with the s orbitals of hydrogen. A vacant p orbital lies perpendicular to the plane of the three C—H bonds.

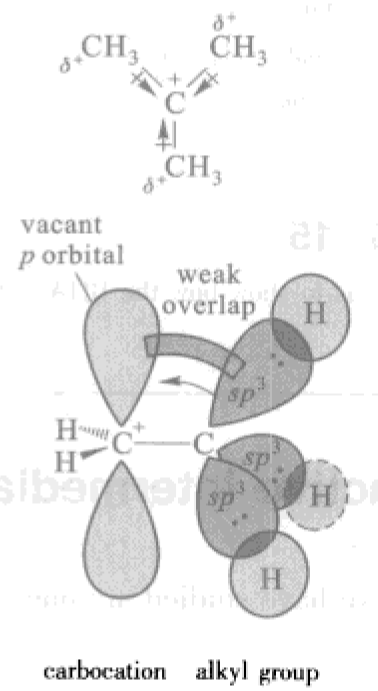
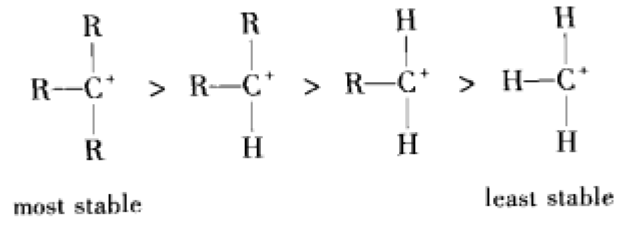


Figure 5–14 Effect of alkyl substituent on carbocation stability. A carbocation is stabilized by overlap of filled orbitals on an adjacent alkyl group with the vacant p orbital of the carbocation. Overlap between a σ bond and a p orbital is called *hyperconjugation* (超共轭).

Like free radicals, carbocations are *electron-deficient* species: They have fewer than eight electrons in the valence shell. Also like free radicals, carbocations, are stabilized by alkyl substituents. An alkyl group stabilizes an electron-deficient carbocation in two ways: (1) through an inductive effect, and (2) through the partial overlap of filled orbitals with empty ones. The **inductive effect** is a donation of electron density through the sigma (σ) bonds of the molecule. The positively charged carbon atom withdraws some electron density from the polarizable alkyl groups bonded to it.

Alkyl substituents also have filled sp^3 orbitals that can overlap with the empty p orbital on the positively charged carbon atom, further stabilizing the carbocation (Figure 5–14). Even though the attached alkyl group rotates, one of its sigma bonds is always aligned with the empty p orbital on the carbocation. The pair of electrons in this σ bond spreads out into the empty p orbital, stabilizing the electron-deficient carbon atom. This type of overlap between a p orbital and a sigma bond is called *hyperconjugation*.

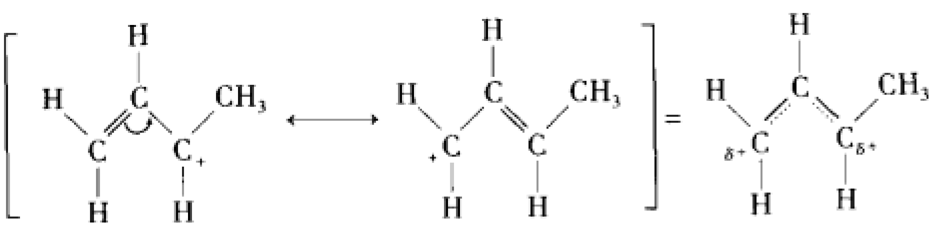
In general, more highly substituted carbocations are more stable.



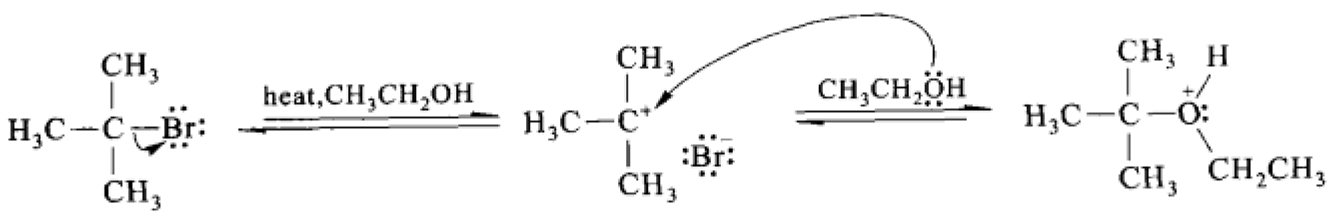
Stability of carbocations

$$3° > 2° > 1° > \text{methyl}$$

Unsaturated carbocations are also stabilized by **resonance stabilization**. If a pi (π) bond is adjacent to a carbocation, the filled p orbitals of the π bond will overlap with the empty p orbital of the carbocation. The result is a delocalized ion, with the positive charge shared by two atoms. Resonance delocalization is particularly effective in stabilizing carbocations.

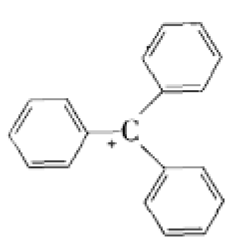


Carbocations are common intermediates in organic reactions. Highly substituted alkyl halides can ionize when they are heated in a polar solvent. The strongly electrophilic carbocation reacts with any available nucleophile, often the solvent.



PROBLEM 5-16

The triphenylmethyl cation is so stable that some of its salts can be stored for months. Explain why this cation is so stable.



triphenylmethyl cation (三苯甲基正离子)

5-16B Free Radicals

Like carbocations, **free radicals** are sp^2 hybridized and planar (or nearly planar). Unlike carbocations, however, the p orbital perpendicular to the plane of the C—H bonds of the radical is not empty; it contains the odd electron. Figure 5-15 shows the structure of the methyl radical.

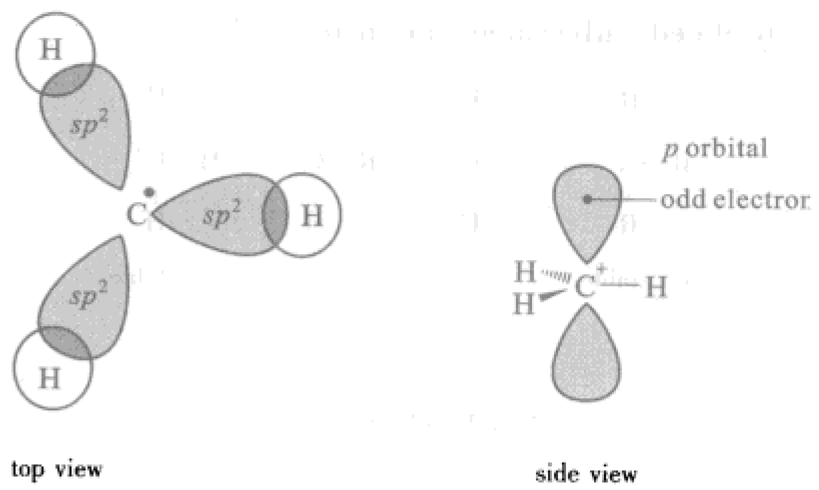
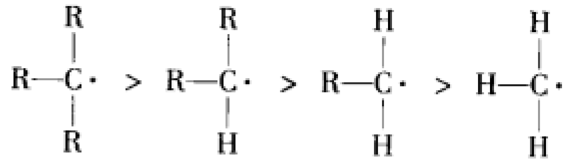


Figure 5–15 Orbital diagram of the methyl radical. The structure of the methyl radical is like that of the methyl cation (Figure 5–13), except there is an additional electron. The odd electron is in the p orbital perpendicular to the plane of the three C—H bonds.

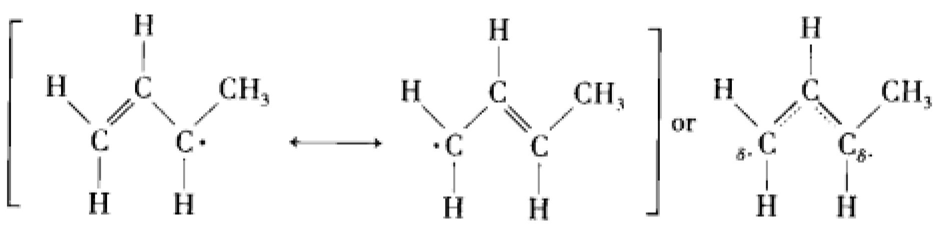
Both radicals and carbocations are electron deficient because they lack an octet around the carbon atom. Like carbocations, radicals are stabilized by the electron-donating effect of alkyl groups, making more highly substituted radicals more stable. This effect is confirmed by the bond-dissociation enthalpies shown in Figure 5–7: Less energy is required to break a C—H bond to form a more highly substituted radical.

Stability of radicals



more stable 3° 2° 1° methyl less stable

Like carbocations, radicals can be stabilized by resonance. Overlap with the p orbitals of a π bond allows the odd electron to be delocalized over two carbon atoms. Resonance delocalization is particularly effective in stabilizing a radical.



5–16C Carbanions

A **carbanion** has a trivalent carbon atom that bears a negative charge. There are eight electrons around the carbon atom (three bonds and one lone pair), so it is not electron deficient; rather, it is electron rich and a strong nucleophile (Lewis base). A carbanion has the same electronic structure as an amine. Compare the structures of a methyl carbanion and ammonia:

methyl anion ammonia

The hybridization and bond angles of a simple carbanion also resemble those of an amine. The carbon atom

is sp^3 hybridized and tetrahedral. One of the tetrahedral positions is occupied by an unshared lone pair of electrons. Figure 5-16 compares the orbital structures and geometry of ammonia and the methyl anion.

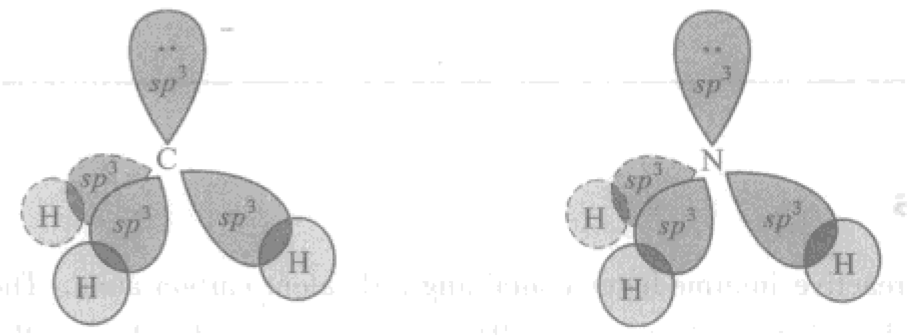
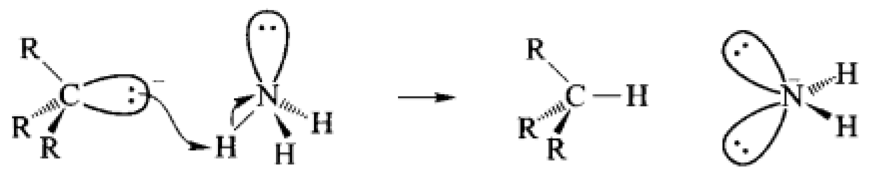


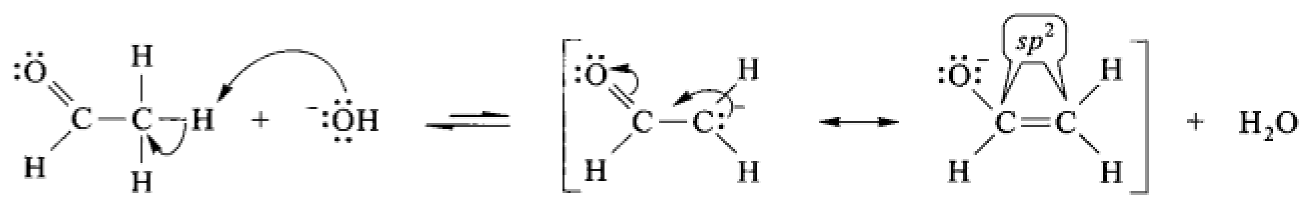
Figure 5-16 Comparison of orbital structures of methyl anion and ammonia. Both the methyl anion and ammonia have an sp^3 hybridized central atom, with a nonbonding pair of electrons occupying one of the tetrahedral positions.

Like amines, carbanions are nucleophilic and basic. A carbanion has a negative charge on its carbon atom, however, making it a more powerful base and a stronger nucleophile than an amine. For example, a carbanion is sufficiently basic to remove a proton from ammonia.



$$R_3C:^- \quad + \quad :NH_3 \quad \longrightarrow \quad R_3CH \quad + \quad ^-:\ddot{N}H_2$$

Carbanions that occur as intermediates in organic reactions are almost always bonded to stabilizing groups. They can be stabilized either by inductive effects or by resonance. For example, halogen atoms are electron withdrawing, so they stabilize carbanions through the inductive withdrawal of electron density. Resonance also plays an important role in stabilizing carbanions. A carbonyl group (C=O) stabilizes an adjacent carbanion by overlap of its π bond with the nonbonding electrons of the carbanion. The negative charge is delocalized onto the electronegative oxygen atom of the carbonyl group.



resonance-stabilized carbanion

This resonance-stabilized carbanion must be sp^2 hybridized and planar for effective delocalization of the negative charge onto oxygen. Resonance-stabilized carbanions are the most common type of carbanions we will encounter in organic reactions.

PROBLEM 5-17

Acetylacetone (2,4-pentanedione) reacts with sodium hydroxide to give water and the sodium salt of a carbanion. Write a complete structural formula for the carbanion, and use resonance forms to show the stabilization of the carbanion.

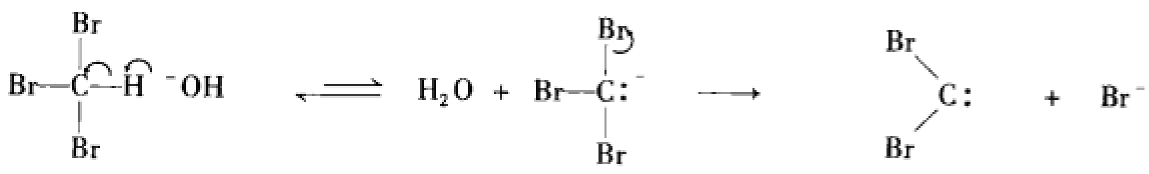
acetylacetone (2,4-pentanedione) (乙酰丙酮)

PROBLEM 5-18

Acetonitrile ($CH_3C{\equiv}N$) is deprotonated by very strong bases. Write resonance forms to show the stabilization of the carbanion that results.

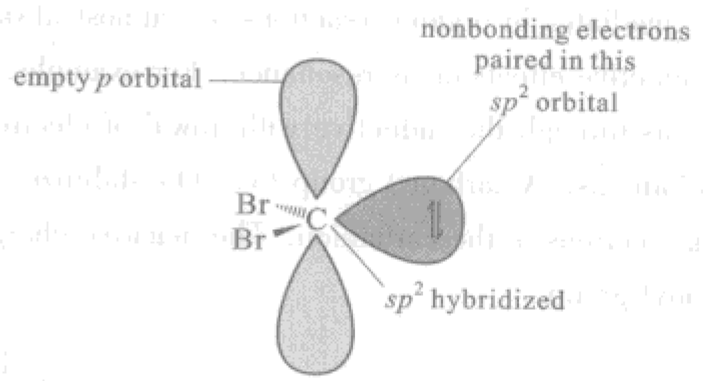
5-16D Carbenes

Carbenes are uncharged reactive intermediates containing a divalent carbon atom. The simplest carbene has the formula: CH_2 and is called *methylene*, just as a $—CH_2—$ group in a molecule is called a *methylene group*. One way of generating carbenes is to form a carbanion that can expel a halide ion. For example, a strong base can abstract a proton from tribromomethane ($CHBr_3$) to give an inductively stabilized carbanion. This carbanion expels bromide ion to give dibromocarbene.

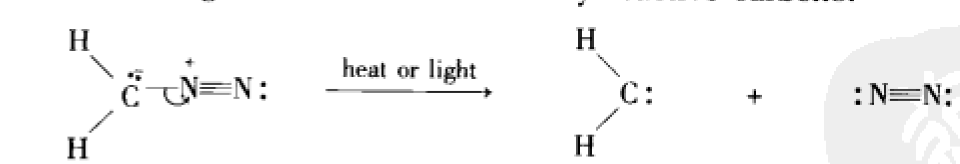


tribromomethane (三溴甲烷) a carbanion dibromocarbene (二溴卡宾)

The electronic structure of dibromocarbene is shown next. The carbon atom has only six electrons in its valence shell. It is sp^2 hybridized, with trigonal geometry. An unshared pair of electrons occupies one of the sp^2 hybrid orbitals, and there is an empty p orbital extending above and below the plane of the atoms. A carbene has both a lone pair of electrons and an empty p orbital, so it can react as a nucleophile or as an electrophile.

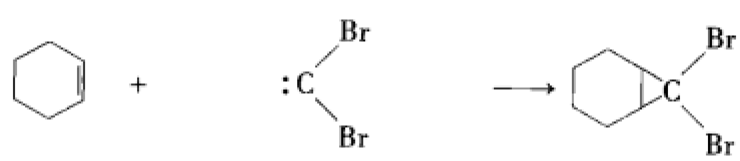


Methylene itself is formed when diazomethane (CH_2N_2) is heated or irradiated with light. The diazomethane molecule splits to form a stable nitrogen molecule and the very reactive carbene.



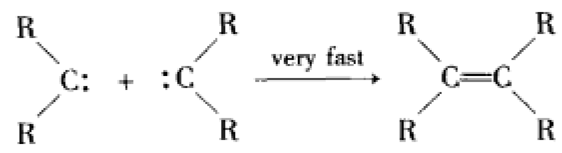
diazomethane (重氮甲烷) methylene (亚甲基) nitrogen

The most common synthetic reaction of carbenes is their addition to double bonds to form cyclopropane rings. For example, dibromocarbene adds to cyclohexene to give an interesting bicyclic compound.



cyclohexene dibromocarbene (二溴卡宾)

No simple carbenes have never been purified or even made in a high concentration, because when two carbenes collide, they immediately dimerize (two of them bond together) to give an alkene.



Carbenes and carbenoids (carbene-like reagents) are useful both for the synthesis of other compounds and for the investigation of reaction mechanisms. The carbene intermediate is generated in the presence of its target compound, so that it can react immediately, and the concentration of the carbene is always low. Reactions using carbenes are discussed in Chapter 9.

Summary in Chinese

本章概要

一、自由基链锁反应机理（the mechanism of free-radical chain reactions）

自由基链锁反应可分为链引发、链增长和链终止三个阶段。一般采用光照、加热或加入自由基引发剂的方法引发产生自由基中间体。在链增长阶段，反应在生成产物的同时不断生成自由基中间体。链增长反应不断循环，直至反应物完全转化或链终止反应使自由基中间体完全失活。

二、热力学与化学平衡（thermodynamics and chemical equilibrium）

1. 热力学研究一个反应能否进行，能进行到什么程度，以及外界条件对化学平衡的影响。化学平衡与反应物和产物的性质、反应条件有关，与反应机理和反应速率无关。

2. 平衡常数（equilibrium constant）为一个可逆反应在一定的反应条件下达到平衡时生成物浓度乘积与反应物浓度乘积之比，用以表示反应进行的程度。对于反应通式

$$aA + bB \longrightarrow cC + dD$$

$$\text{平衡常数为：} K_{eq} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

3. 标准自由能变化（standard Gibbs free energy change，$\Delta G^{\ominus}$）：表示在标准状态下产物与反应物自由能之差。自由能变化与平衡常数的关系如下：

$$K_{eq} = e^{-\Delta G^{\ominus}/(RT)} \text{ 或 } \Delta G^{\ominus} = -2.303\,RT(\lg K_{eq})$$

式中：R 为摩尔气体常数；T 为反应时的热力学温度。

$\Delta G^{\ominus}$ 为负值时，$K_{eq} > 1$，反应平衡位置趋向于产物；而 $\Delta G^{\ominus}$ 为正值时，$K_{eq} < 1$，平衡位置趋向于反应物。

4. 焓变（enthalpy，$\Delta H^{\ominus}$）与熵变（entropy，$\Delta S^{\ominus}$）：$\Delta H^{\ominus}$ 为在标准状态下产物与反应物热焓之差，即一个反应吸收或释放的反应热，可通过反应物和产物分子中键的解离能进行计算。共价键均裂所需提供的能量称为键解离能（bond-dissociation energy）。计算所得 $\Delta H^{\ominus}$ 为负值时，反应放热（exothermic）；反之，$\Delta H^{\ominus}$ 为正值时，反应吸热（endothermic）。熵表示反应体系内的无序程度，$\Delta S^{\ominus}$ 为在标准状态下产物与反应物熵之差，即反应过程中体系内无序程度的变化。$\Delta S^{\ominus}$ 为正值时，无序程度增加；反之，$\Delta S^{\ominus}$ 为负值时，无序程度减小、反应自由能变化与焓变、熵变的关系如下：

$$\Delta G^{\ominus} = \Delta H^{\ominus} - T\Delta S^{\ominus}$$

在许多有机反应中，与 $\Delta H^{\ominus}$ 相比，$\Delta S^{\ominus}$ 很小，可以忽略不计，此时 $\Delta G^{\ominus} \approx \Delta H^{\ominus}$。

三、动力学与反应速率（kinetics and reaction rate）

1. 动力学研究反应进行的速率及反应条件对反应速率的影响，研究反应机理，从而确定决定反应速

率的关键步骤。催化剂能够加快反应速率，但不能改变化学平衡。

2. 反应速率与反应物浓度的乘积成正比，对于以下反应通式

$$A + B \longrightarrow C + D$$

反应速率公式为： $r = k_r[A]^a[B]^b$

式中：k_r 为速率常数，直接体现反应速率的快慢和反应的难易，反应条件和催化剂都可影响速率常数；幂值 a 和 b 分别为反应对于反应物 A 和 B 的级数，反应总级数 $= a + b$。基元反应的速率公式和反应级数可直接从化学反应式得到，多为一级或二级反应。非基元反应的级数必须通过实验测得。反应对于各个反应物的级数能够为研究反应机理提供十分有用的信息。

3. 过渡态(transition state)：反应进行时，反应物分子达到的最高能量状态称为过渡态。在过渡态中旧键部分断裂，新键部分形成。过渡态不同于中间体，过渡态为高活性物种，瞬间即逝，无法分离。

4. 活化能(activation energy, E_a)：活化能为分子彼此碰撞时克服电子云之间的斥力，达到活化状态所需要的最小能量，即过渡态与反应物之间的能量差。活化能与速率常数和反应温度的关系可用阿仑尼乌斯方程(Arrhenius equation)表示。

$$k_r = Ae^{-E_a/(RT)} \text{（}A\text{ 为常数，频率因子）}$$

活化能越小，反应速率越快。对于多步反应来说，活化能最高的步骤反应速率最慢，决定了多步反应的总反应速率，称为速率决定步骤(rate-determining step)。

四、Hammond 假说与反应选择性(the Hammond postulate and selectivity in reaction)

1. Hammond 假说：能量上接近的相关联物种在结构上亦接近。过渡态的结构和与其能量上最接近的稳定物种的结构相似。

2. 反应选择性：根据 Hammond 假说可以推测反应的选择性。在吸热反应中，产物或中间体的能量高于反应物，过渡态的能量与产物或中间体的能量较接近，因此其结构与产物或中间体的结构相似，从而使不同过渡态的能量差增大，反应选择性提高；而在放热反应中，产物或中间体的能量低于反应物，此时过渡态的能量与反应物的能量较接近，其结构与反应物的结构相似，使不同过渡态的能量差减小，反应选择性降低。烷烃溴代反应中生成碳自由基中间体的反应是吸热的，因此溴代对于烷烃中不同的 C—H 键具有很高的选择性，而氯代反应中生成碳自由基中间体的反应是少量放热的，对于不同的 C—H 键只有中等选择性。

五、活泼中间体(reactive intermediates)

除一步反应之外，反应过程都要经过活泼中间体。有机反应中重要的活泼中间体包括碳正离子(carbocation)、碳自由基(carbon free radical)、碳负离子(carbanion)和卡宾(carbene)。这些活泼中间体的结构、性质、中心碳的杂化态、未成键电子数和稳定性见下表。共振效应可使碳正离子、碳自由基和碳负离子稳定，取代基给电子诱导效应(electron-donating inductive effect)可稳定碳正离子，而具有吸电子诱导效应(electron-withdrawing inductive effect)的取代基可使碳负离子稳定。

名称	结构	杂化态	未成键电子数	性质	稳定性
碳正离子	$-\overset{|}{\underset{|}{C}}{}^{+}$	sp^2	0	缺电子，可作为亲电性强酸	$3°C^+ > PhCH_2^+ > H_2C=CHCH_2^+ > 2°C^+ > 1°C^+ > {}^+CH_3$
碳自由基	$-\overset{|}{\underset{|}{C}}\cdot$	sp^2	1	缺电子	$PhCH_2\cdot > CH_2=CHCH_2\cdot > 3°C\cdot > 2°C\cdot > 1°C\cdot > \cdot CH_3$

续表

名称	结构	杂化态	未成键电子数	性质	稳定性
碳负离子	$-\overset{\vert}{\underset{\vert}{C}}:^-$	sp^3	2	富电子，可作为亲核性强碱	$^-:CH_3 > 1°C^- > 2°C^- > 3°C^-$
卡宾	$>C:$	sp^2	2	既有亲核性亦有亲电性	

Essential Problem-Solving Skills in Chapter 5

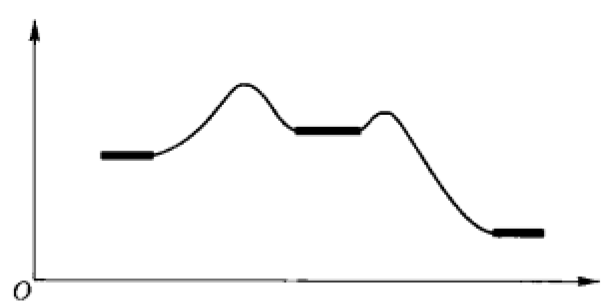
1. Explain the mechanism and energetics of the free-radical halogenation of alkanes.
2. Based on the selectivity of halogenation, predict the products of halogenation of an alkane.
3. Calculate free-energy changes from equilibrium constants.
4. Calculate enthalpy changes from bond-dissociation enthalpies.
5. Determine the order of a reaction, and suggest a possible mechanism based on its rate equation.
6. Use energy diagrams to discuss transition states, activation energies, intermediates, and the rate-determining step of a multistep reaction.
7. Use the Hammond postulate to predict whether a transition state will be reactant-like or product-like.
8. Describe the structures of carbocations, carbanions, free radicals, and carbenes and the structural features that stabilize them. Explain which are electrophilic and which are nucleophilic.

Study Problems

5-19 Define and give an example for each term.

(a) homolytic cleavage（均裂） (b) heterolytic cleavage（异裂） (c) free radical（自由基）
(d) carbocation（碳正离子） (e) carbanion（碳负离子） (f) carbene（卡宾）
(g) carbonium ion（碳正离子） (h) intermediate（中间体） (i) catalyst（催化剂）
(j) transition state（过渡态） (k) rate equation（速率公式） (l) equilibrium constant（平衡常数）
(m) rate constant（速率常数） (n) reaction mechanism（反应机理） (o) chain reaction（链反应）
(p) substitution reaction（取代反应） (q) activation energy（活化能） (r) bond-dissociation enthalpy（键解离焓）
(s) rate-limiting step（速率决定步骤） (t) Hammond postulate (u) resonance stabilization（共振稳定化作用）

5-20 Consider the following reaction-energy diagram.

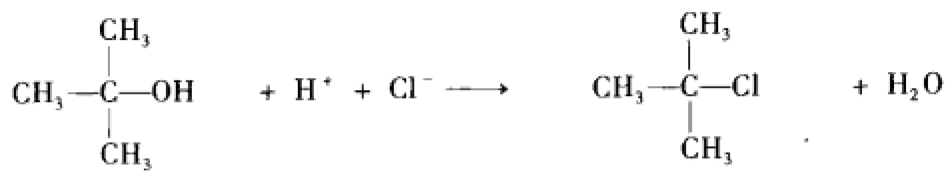


(a) Label the reactants and the products. Label the activation energy for the first step and the second step.
(b) Is the overall reaction endothermic or exothermic? What is the sign of $\Delta H^\ominus$?
(c) Which points in the curve correspond to intermediates? Which correspond to transition states?

(d) Label the transition state of the rate-limiting step. Does its structure resemble the reactants, the products, or an intermediate?

5–21 Draw a reaction-energy diagram for a two-step endothermic reaction with a rate-limiting second step.

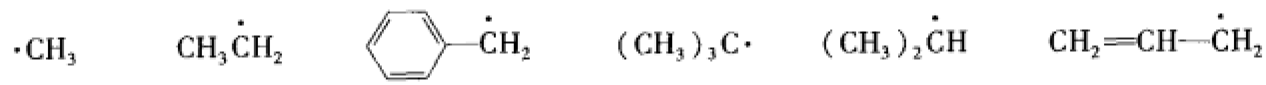
5–22 Treatment of *t*-butyl alcohol with concentrated HCl gives *t*-butyl chloride.



t-butyl alcohol（叔丁醇） *t*-butyl chloride（叔丁基氯）

When the concentration of H^+ is doubled, the reaction rate doubles. When the concentration of *t*-butyl alcohol is tripled, the reaction rate triples. When the chloride ion concentration is quadrupled, however, the reaction rate is unchanged. Write the rate equation for this reaction.

5–23 Use the information in Table 5–2 to rank the following radicals in decreasing order of stability.

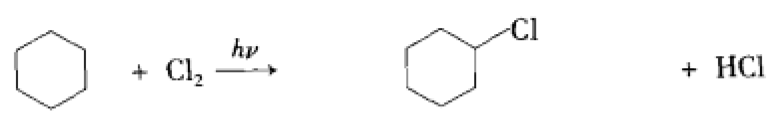


5–24 For each of the following alkanes,

1. Draw all the possible monochlorinated derivatives.
2. Determine whether free-radical chlorination would be a good way to make any of these monochlorinated derivatives.
3. Which monobrominated derivatives could you form in good yield by free-radical bromination?

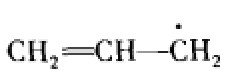
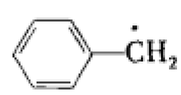
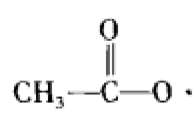
(a) cyclopentane (b) methylcyclopentane
(c) 2,3-dimethylbutane (d) 2,2,3,3-tetramethylbutane

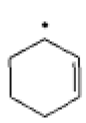
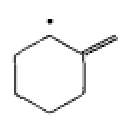
5–25 Write a mechanism for the light-initiated reaction of cyclohexane with chlorine to give chlorocyclohexane. Label the initiation and propagation steps.



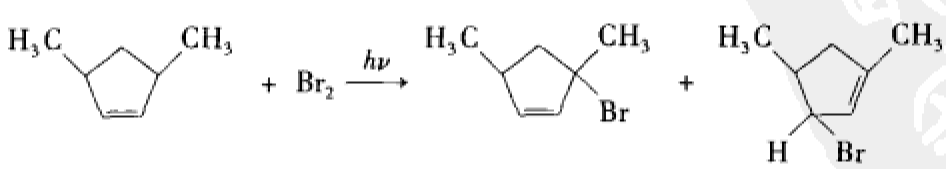
cyclohexane chlorocyclohexane（氯代环己烷）

5–26 Draw the important resonance structures of the following free radicals.

(a)  (b)  (c) 

(d)  (e) 

***5–27** In the presence of a small amount of bromine, the following light-promoted reaction has been observed.

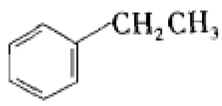


(a) Write a mechanism for this reaction. Your mechanism should explain how both products are formed. (*Hint*: Notice which H atom has been lost in both products.)

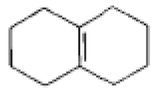
(b) Explain why only this hydrogen atom has been replaced, in preference to any of the other hydrogen atoms in the starting maerial.

5–28 For each compound, predict the major product of free-radical bromination. Remember that bromination is highly selective, and only the most stable radical will be formed.

(a) cyclohexane (b) methylcyclopentane (c) 2,2,3-trimethylbutane
(d) decalin (e) 3-methyloctane (f) hexane

(g) 

ethylbenzene (乙苯)

(h)  (2 products)

5−29 When exactly 1 mole of methane is mixed with exactly 1 mole of chlorine and light is shone on the mixture, a chlorination reaction occurs. The products are found to contain substantial amounts of di-, tri-, and tetrachloromethane.

(a) Explain how a mixture is formed from this stoichiometric mixture of reactants, and propose mechanisms for the formation of these compounds from chloromethane.

(b) How would you run this reaction to get a good conversion of methane to CH_3Cl? Methane to CCl_4?

5−30 The chlorination of pentane gives a mixture of three monochlorinated products.

(a) Draw their structures.

(b) Predict the ratios in which these monochlorination products will be formed, remembering that a chlorine atom abstracts a secondary hydrogen about 4.5 times as fast as it abstracts a primary hydrogen.

5−31 (a) Draw the structure of the transition state for the second propagation step in the chlorination of methane.

$$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$

Show whether the transition state is product-like or reactant-like, and which of the two partial bonds is stronger.

(b) Repeat for the second propagation step in the bromination of methane.

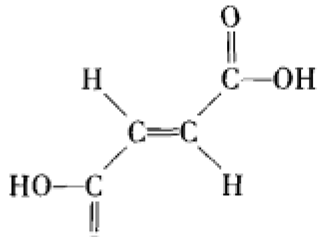
5−32 Peroxides are often added to free-radical reactions as initiators because the oxygen-oxygen bond is homolytically cleaved rather easily. For example, the bond-dissociation enthalpy of the O—O bond in hydrogen peroxide (H—O—O—H) is only 212 kJ/mol. Give a mechanism for the hydrogen peroxide-initiated reaction of cyclopentane with chlorine.

Chapter 6
Stereochemistry

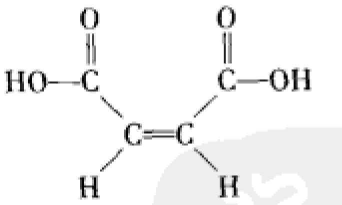
6-1 Introduction

Stereochemistry is the study of the three-dimensional structure of molecules. No one can understand organic chemistry, biochemistry, or biology without using stereochemistry. Biological systems are exquisitely selective, and they often discriminate between molecules with subtle stereochemical differences. We have seen (Section 2-8) that isomers are grouped into two broad classes: constitutional isomers and stereoisomers. **Constitutional isomers** (**structural isomers**) differ in their bonding sequence; their atoms are connected differently. **Stereoisomers** have the same bonding sequence, but they differ in the orientation of their atoms in space.

Differences in spatial orientation might seem unimportant, but stereoisomers often have remarkably different physical, chemical, and biological properties. For example, the cis and trans isomers of butenedioic acid are a special type of stereoisomer called *cis-trans isomers* (or *geometric isomers*). Both compounds have the formula HOOC—CH=CH—COOH, but they differ in how these atoms are arranged in space. The cis isomer is called *maleic acid*, and the trans isomer is called *fumaric acid*. Fumaric acid is an essential metabolic intermediate in both plants and animals, but maleic acid is toxic and irritating to tissues.



fumaric acid (富马酸), mp 287 ℃
essential metabolite



maleic acid (马来酸), mp 138 ℃
toxic irritant

The discovery of stereochemistry was one of the most important breakthroughs in the structural theory of organic chemistry. Stereochemistry explained why several types of isomers exist, and it forced scientists to propose the tetrahedral carbon atom. In this chapter, we study the three-dimensional structures of molecules to understand their stereochemical relationships. We compare the various types of stereoisomers and study ways to differentiate among stereoisomers. In future chapters, we will see how stereochemistry plays a major role in the properties and reactions of organic compounds.

6−2 Chirality

What is the difference between your left hand and your right hand? They look similar, yet a left-handed glove does not fit the right hand. The same principle applies to your feet. They look almost identical, yet the left shoe fits painfully on the right foot. The relationship between your two hands or your two feet is that they are nonsuperimposable (nonidentical) mirror images of each other. Objects that have left-handed and right-handed forms and called **chiral** (*ki'rel*, rhymes with "spiral"), the Greek word for "handed."

We can tell whether an object is chiral by looking at its mirror image (Figure 6−1). Every physical object (with the possible exception of a vampire) has a mirror image, but *a chiral object has a mirror image that is different from the original object.* For example, a chair and a spoon and a glass of water all look the same in a mirror. Such objects are called **achiral**, meaning "not chiral." A hand looks different in the mirror. If the original hand were the right hand, it would look like a left hand in the mirror.

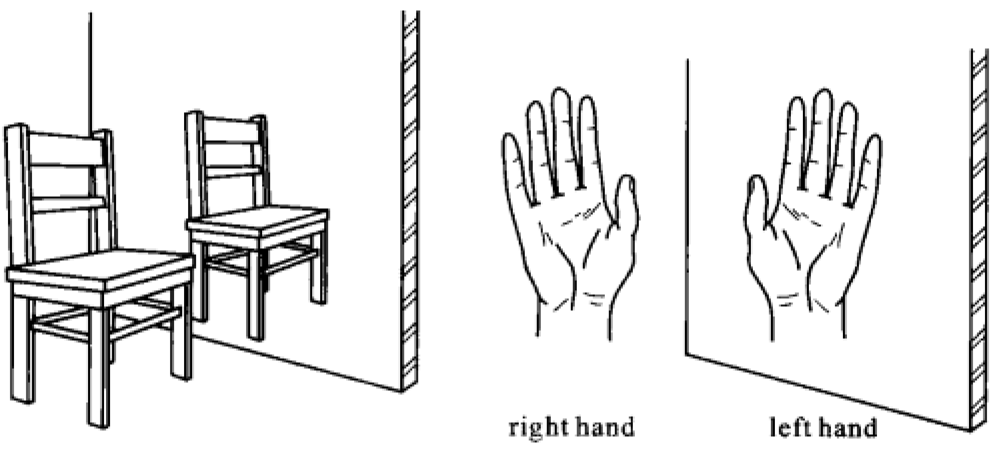
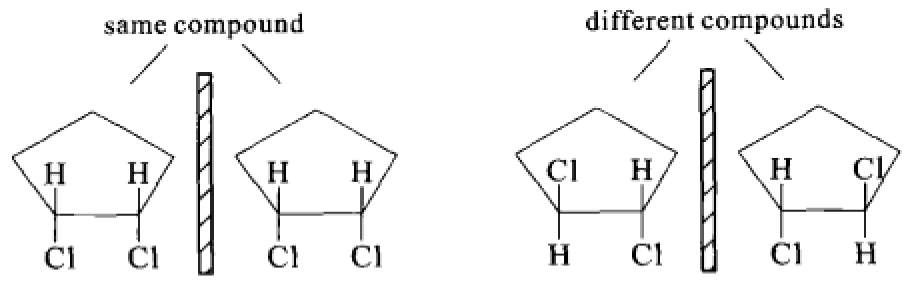


Figure 6−1 Use of a mirror to test for chirality. An object is chiral if its mirror image is different from the original object.

6−2A Chirality and Enantiomerism in Organic Molecules

Like other objects, molecules are either chiral or achiral. For example, consider the two geometric isomers of 1,2-dichlorocyclopentane (Figure 6−2). The cis isomer is achiral because its mirror image is superimposable on the original molecule. Two molecules are said to be **superimposable** if they can be placed on top of each other and the three-dimensional position of each atom of one molecule coincides with the equivalent atom of the other molecule. To draw the mirror image of a molecule, simply draw the same structure with left and right reversed. The up-and-down and front-and-back directions are unchanged. These two mirror-image structures are identical (superimposable), and *cis*-1,2-dichlorocyclopentane is achiral.

The mirror image of *trans*-1,2-dichlorocyclopentane is different from (nonsuperimposable with) the original molecule. These are two different compounds, and we should expect to discover two mirror-image isomers of *trans*-1,2-dichlorocyclopentane. Make models of these isomers to convince yourself that they are different no matter how you twist and turn them. Nonsuperimposable mirror-image molecules are called **enantiomers**. A chiral compound always has an enantiomer (a nonsuperimposable mirror image). An achiral compound always has a mirror image that is the same as the original molecule. Let's review the definitions of these words.



cis-1, 2-dichlorocyclopentane (achiral) *trans*-1, 2-dichlorocyclopentane (chiral)

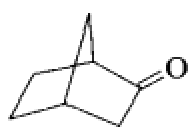
Figure 6−2 Stereoisomers of 1,2-dichlorocyclopentane. The cis isomer has no enantiomers; it is achiral. The trans isomer is chiral; it can exist in either of two nonsuperimposable enantiomeric forms.

enantiomers: mirror-image isomers; pairs of compouds that are nonsuperimposable mirror images
(对映体)
chiral: ("handed") different from its mirror image; having an enantiomer
(手性)
achiral: ("not handed") identical with its mirror image; not chiral
(非手性)

Any compound that is chiral must have an enantiomer. Any compound that is achiral cannot have an enantiomer.

PROBLEM 6−1

Make a model and draw a three-dimensional structure for each compound. Then draw the mirror image of your original structure and determine whether the mirror image is the same compound. Label each structure as being chiral or achiral, and label pairs of enantiomers.

(**a**) *cis*-1,2-dimethylcyclobutane
(**b**) *trans*-1,2-dimethylcyclobutane
(**c**) *cis*-and *trans*-1,3-dimethylcyclobutane
(**d**) 2-bromobutane
(**e**) 

(**f**)

6−2B Asymmetric Carbon Atoms, Chirality Centers, and Stereocenters

The three-dimensional drawing of 2-bromobutane in Figure 6−3 shows that 2-bromobutane cannot be superimposed on its mirror image. This simple molecule is chiral, with two distinct enantiomers. What is it about a molecule that makes it chiral? The most common feature (but not the only one) that lends chirality is a carbon atom that is bonded to four different groups. Such a carbon atom is called an **asymmetric carbon atom** or a **chiral carbon atom**, and is often designated by an asterisk(*). Carbon atom 2 of 2-bromobutane is bonded to a hydrogen atom, a bromine atom, a methyl group, and an ethyl group. It is an asymmetric carbon atom, and it is responsible for the chirality of 2-bromobutane.

An asymmetric carbon atom is the most common example of a **chirality center**, the IUPAC term for any atom holding a set of ligands in a spatial arrangement that is not superimposable on its mirror image. Chirality centers belong to an even broader group called *stereocenters*. A **stereocenter** (or **stereogenic atom**) is any atom at which the interchange of two groups gives a stereoisomer. Asymmetric carbons and the double-bonded carbon at-

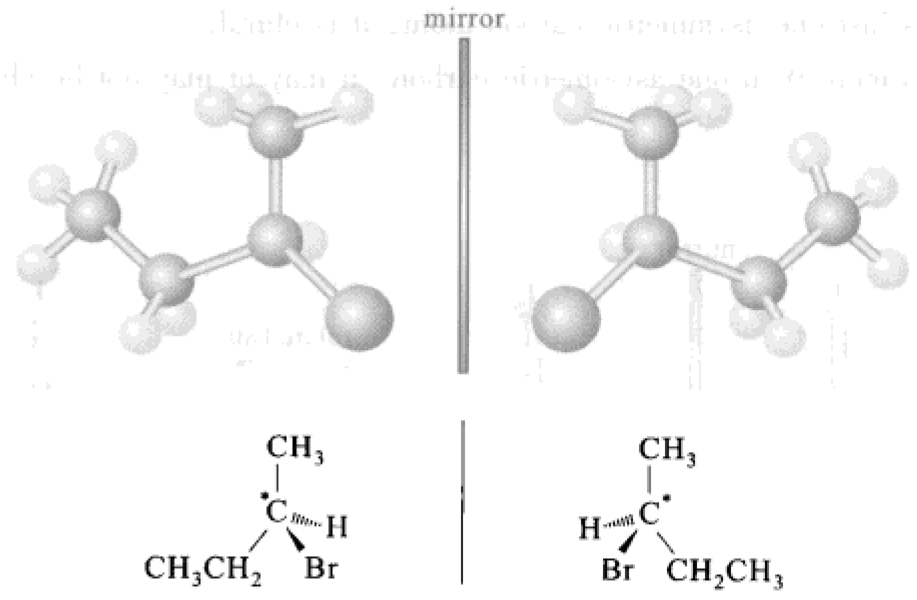


Figure 6-3 2-Bromobutane is chiral by virtue of an asymmetric carbon atom (chiral carbon atom), marked by an *.

oms in cis-trans isomers are the most common types of stereocenters. Figure 6-4 compares these successively broader definitions.

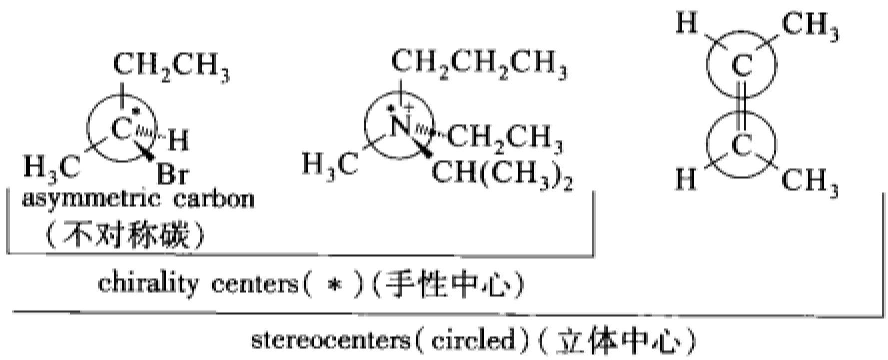


Figure 6-4 Asymmetric carbon atoms are examples of chirality centers, which are examples of stereocenters.

Make a model of an asymmetric carbon atom, bonded to four different atoms. Also make its mirror image, and try to superimpose the two (Figure 6-5). No matter how you twist and turn the models, they never look exactly the same.

If two of the four groups on a carbon atom are the same, however, the arrangement usually is not chiral. Figure 6-6 shows the mirror image of a tetrahedral structure with only three different groups; two of the four groups are the same. If the structure on the right is rotated 180°, it can be superimposed on the left structure.

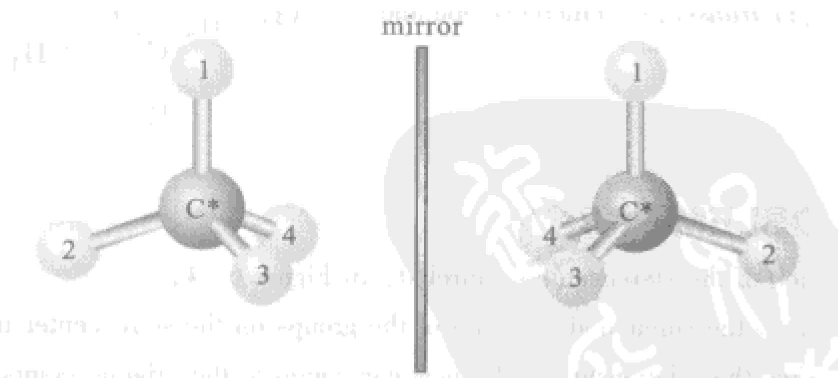


Figure 6-5 Enantiomers of an asymmetric carbon atom. These two mirror images are nonsuperimposable.

We can generalize at this point, but keep in mind that the ultimate test for chirality is always whether the molecule's mirror image is the same or different.

1. If a compound has no asymmetric carbon atom, it is usually achiral.

2. If a compound has just one asymmetric carbon atom, it is chiral.

3. If a compound has more than one asymmetric carbon, it may or may not be chiral. (We will see examples in Section 6-11.)

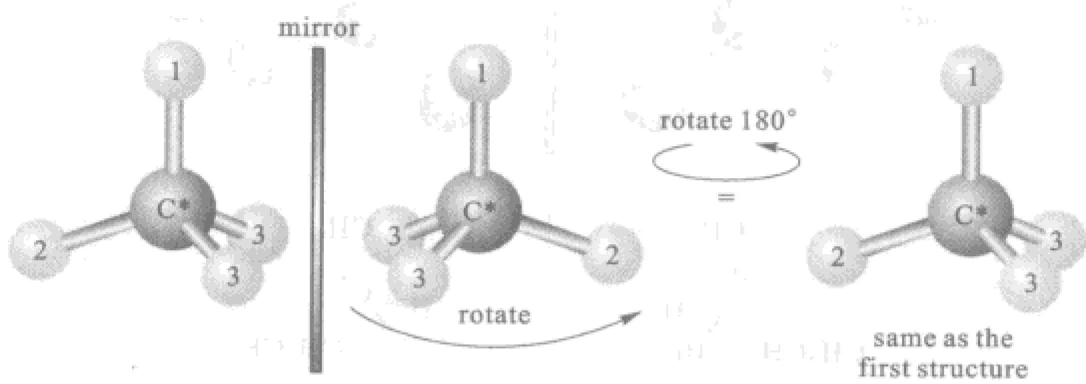


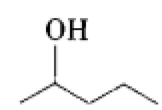
Figure 6-6 A carbon atom bonded to just three different types of groups is not chiral.

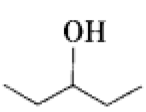
PROBLEM 6-2

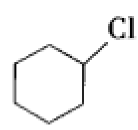
Draw a three-dimensional structure for each compound, and star all asymmetric carbon atoms. Draw the mirror image for each structure, and state whether you have drawn a pair of enantiomers or just the same molecule twice. Build molecular models of any of these examples that seem difficult to you.

(a)
1-bromobutane

(b)
1-pentanol

(c) 
2-pentanol

(d) 
3-pentanol

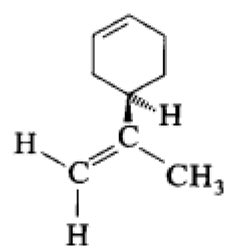
(e) 
chlorocyclohexane

(f) $CH_3-CH(NH_2)-COOH$

(g) *cis*-1,2-dichlorocyclobutane

(h) *trans*-1,2-dichlorocyclobutane

(i) *trans*-1,3-dichlorocyclobutane

(j) 

(k)

PROBLEM 6-3

For each of the stereocenters (circled) in Figure 6-4,

(a) draw the compound with two of the groups on the stereocenter interchanged.

(b) give the relationship of the new compound to the original compound.

6-2C Mirror Planes of Symmetry

In Figure 6-2 we saw that *cis*-1,2-dichlorocyclopentane is achiral. Its mirror image was found to be identical with the original molecule. Figure 6-7 shows a shortcut that often shows whether a molecule is chiral. If we draw

a line down the middle of *cis*-1,2-dichlorocyclopentane, bisecting a carbon atom and two hydrogen atoms, the part of the molecule that appears to the right of the line is the mirror image of the part on the left. This kind of symmetry is called an **internal mirror plane**, sometimes symbolized by the Greek lowercase letter sigma (σ). Since the right-hand side of the molecule is the reflection of the left-hand side, the molecule's mirror image is the same as the original molecule.

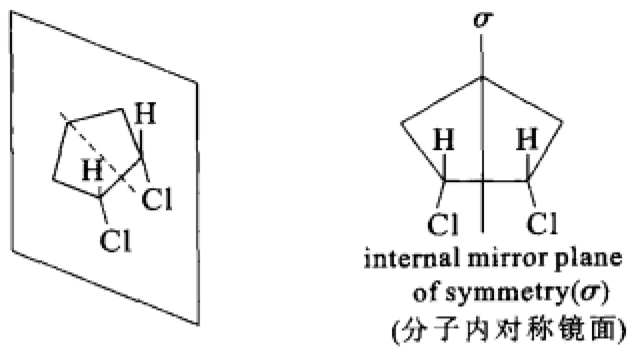
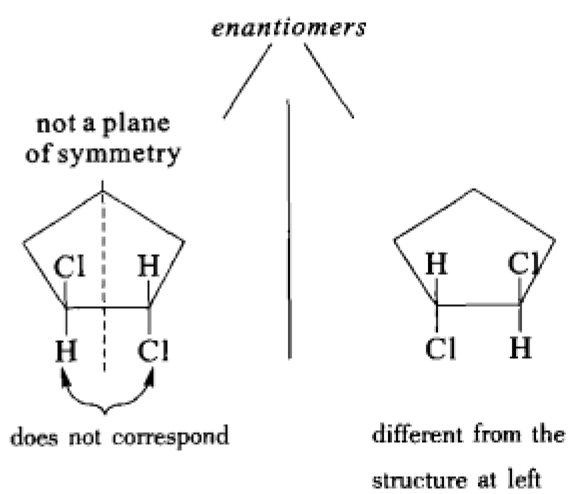


Figure 6-7 Internal mirror plane. *cis*-1,2-Dichlorocyclopentane has an internal mirror plane of symmetry. Any compound with an internal mirror plane of symmetry *cannot* be chiral.

Notice in the following figure that the chiral trans isomer of 1,2-dichlorocyclopentane does not have a mirror plane of symmetry. The chlorine atoms do not reflect into each other across our hypothetical mirror plane. One of them is directed up, the other down.



We can generalize from these and other examples to state the following principle:

Any molecule that has an internal mirror plane of symmetry cannot be chiral, even though it may contain asymmetric carbon atoms.

The converse is not true, however. When we cannot find a mirror plane of symmetry, that does not ne-cessarily mean that the molecule must be chiral. The following example has no internal mirror plane of symmetry, yet the mirror image is superimposable on the original molecule. You may need to make models to show that these mirror images are just two drawings of the same compound.

(hydrogens are omitted for clarity)

PROBLEM 6-4

For each compound, determine whether the molecule has an internal mirror plane of symmetry. If it does, draw the mirror plane on a three-dimensional drawing of the molecule. If the molecule does not have an internal mirror plane, determine whether or not the structure is chiral.

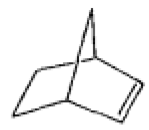
(a) methane

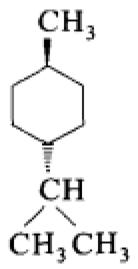
(b) *cis*-1,2-dibromocyclobutane

(c) *trans*-1,2-dibromocyclobutane

(d) 1,2-dichloropropane

(e) glyceraldehyde, HOCH$_2$—CH(OH)—CHO

(f) 

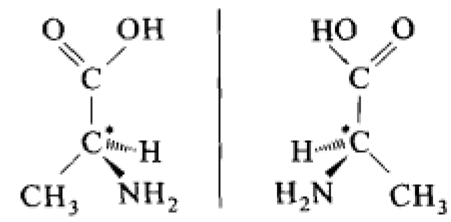
(g) 

(h) CH_3—CH(NH_2)—COOH

alanine（丙氨酸）

6-3 (*R*) and (*S*) Nomenclature of Asymmetric Carbon Atoms

Alanine, from Problem 6-4 (h), is one of the amino acids found in common proteins. Alanine has an asymmetric carbon atom, and it exists in two enantiomeric forms.



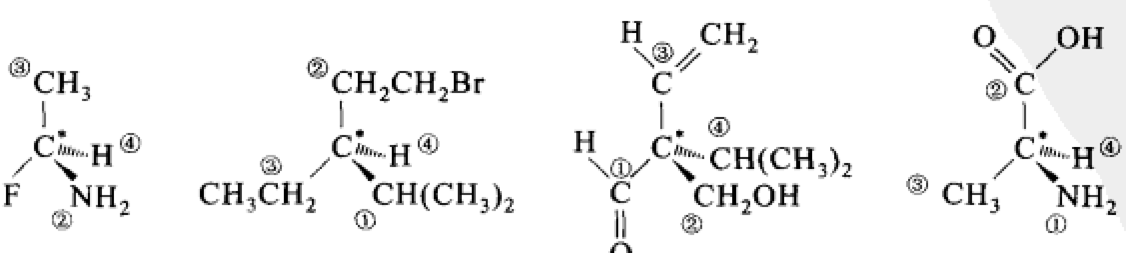
natural alanine　　unnatural alanine

These mirror images are different, and this difference is reflected in their biochemistry. Only the enantiomer on the left can be metabolized by the usual enzyme; the one on the right is not recognized as a useful amino acid. Both are named alanine, however, or 2-aminopropanoic acid in the IUPAC system. We need a simple way to distinguish between enantiomers and to give each of them a unique name.

The difference between the two enantiomers of alanine lies in the three-dimensional arrangement of the four groups around the asymmetric carbon atom. Any asymmetric carbon has two possible (mirror-image) spatial arrangements, which we call **configurations.** The alanine enantiomers represent the two possible arrangements of its four groups around the asymmetric carbon atom. If we can name the two configurations of any asymmetric carbon atom, then we have a way of specifying and naming the enantiomers of alanine or any other chiral compound.

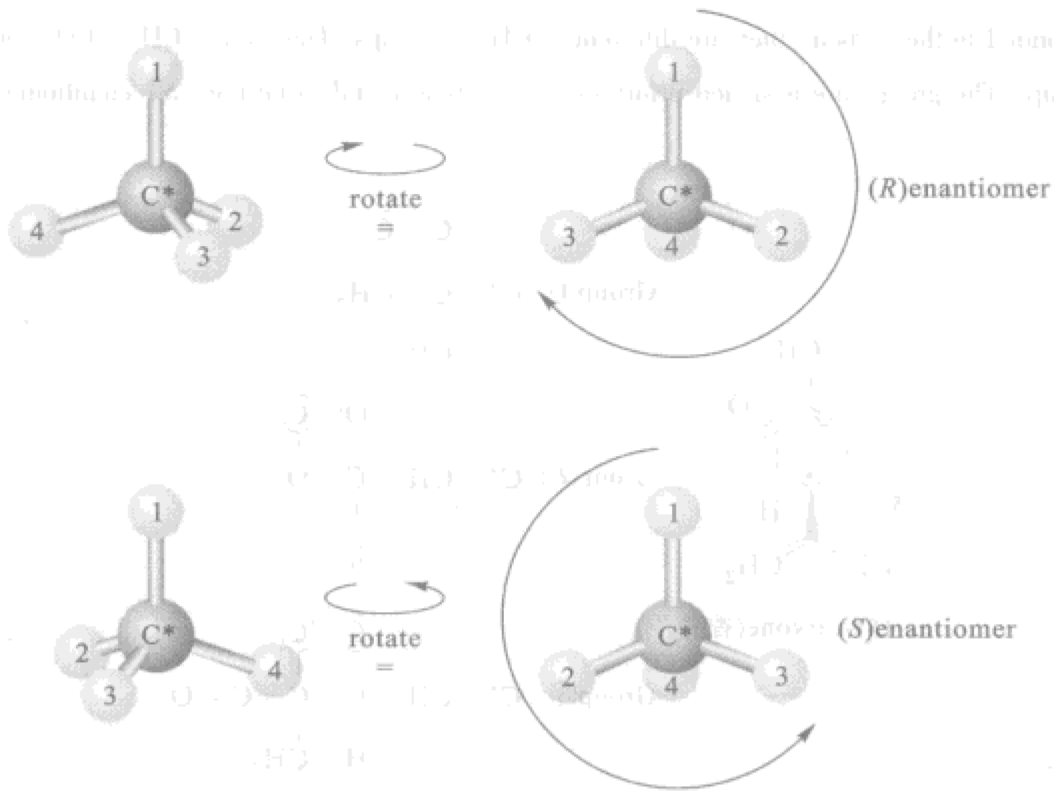
The **Cahn-Ingold-Prelog convention** (Section 3-5C) is the most widely accepted system for naming the configurations of chirality centers. Each asymmetric carbon atom is assigned a letter (*R*) or (*S*) based on its three-dimensional configuration. To determine the name, we follow a two-step procedure that assigns "priorities" to the four substituents and then assigns the name based on the positions of these substituents. Here is the procedure:

1. *Assign a "priority" to each group bonded to the asymmetric carbon.* We speak of group 1 as having the highest priority, group 2 second, group 3 third, and group 4 as having the lowest priority.



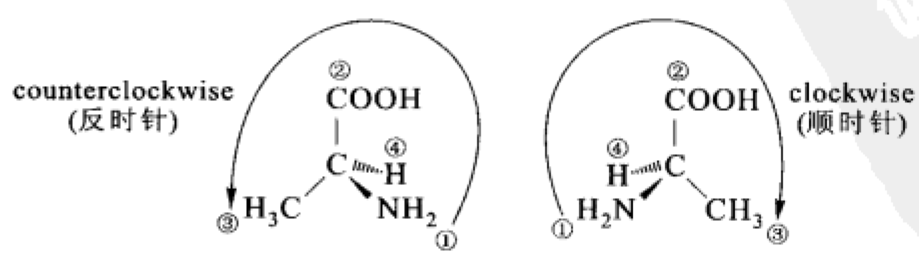
alanine

2. *Using a three-dimensional drawing or a model, put the fourth-priority group in back and view the molecule along the bond from the asymmetric carbon to the fourth-priority group. Draw an arrow from the first-priority group, through the second, to the third.* If the arrow points clockwise, the asymmetric carbon atom is called (*R*) (Latin, *rectus*, "upright"). If the arrow points counterclockwise, the chiral carbon atom is called (*S*) (Latin, *sinister*, "left").



Alternatively, you can draw the arrow and imagine turning a car's steering wheel in that direction. If the car would go to the left, the asymmetric carbon atom is designated (*S*). If the car would go to the right, the asymmetric carbon atom is designated (*R*).

Let's use the enantiomers of alanine as an example. The naturally occurring enantiomer is the one on the left, determined to have the (*S*) configuration. Of the four atoms attached to the asymmetric carbon in alanine, nitrogen has the largest atomic number, giving it the highest priority. Next is the —COOH carbon atom, since it is bonded to oxygen atoms. Third is the methyl group, followed by the hydrogen atom. When we position the natural enantiomer with its hydrogen atom pointing away from us, the arrow from $—NH_2$ to —COOH to $—CH_3$ points counterclockwise. Thus, the naturally occurring enantiomer of alanine has the (*S*) configuration. Make models of these enantiomers to illustrate how they are named (*R*) and (*S*). Notice that interchanging any two substituents on an asymmetric carbon atom inverts its (*R*) or (*S*) configuration. If there is only one asymmetric carbon in a molecule, inverting its configuration gives the enantiomer.

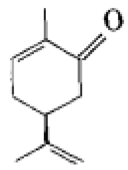


natural (*S*)-alanine   unnatural (*R*)-alanine

SOLVED PROBLEM 6−1

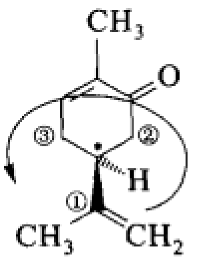
The structure of one of the enantiomers of carvone is shown here. Find the asymmetric carbon atom, and determine whether it

has the (R) or the (S) configuration.

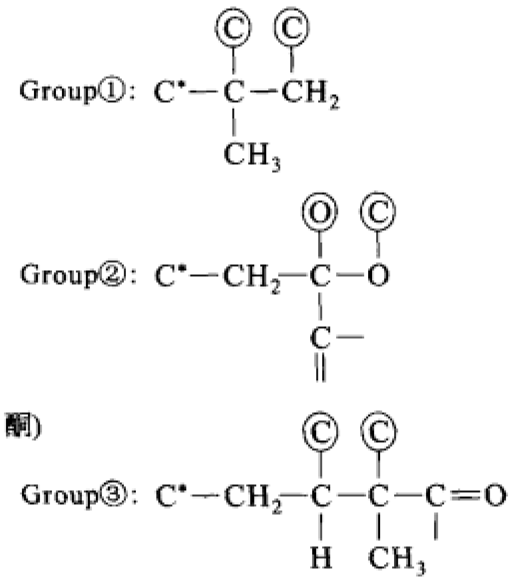


SOLUTION

The asymmetric carbon atom is one of the ring carbons, as indicated by the asterisk in the following structure. Although there are two $-CH_2-$ groups bonded to the carbon, they are different $-CH_2-$ groups. One is a $-CH_2-CO-$ group, and the other is a $-CH_2-CH=C$ group. The groups are assigned priorities, and this is found to be the (S) enantiomer.

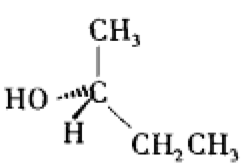


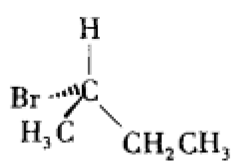
(S)-carvone(香芹酮)

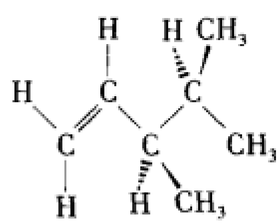


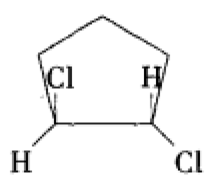
PROBLEM 6-5

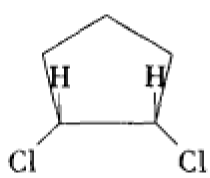
Star (*) each asymmetric carbon atom in the following examples, and determine whether it has the (R) or (S) configuration.

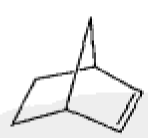
(a) 

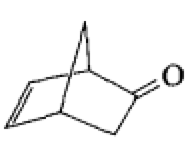
(b) 

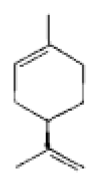
(c) 

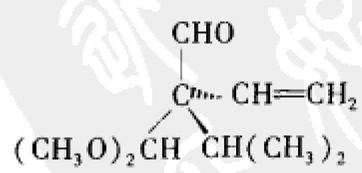
(d) 

(e) 

(f) 

(g) 

(h) 

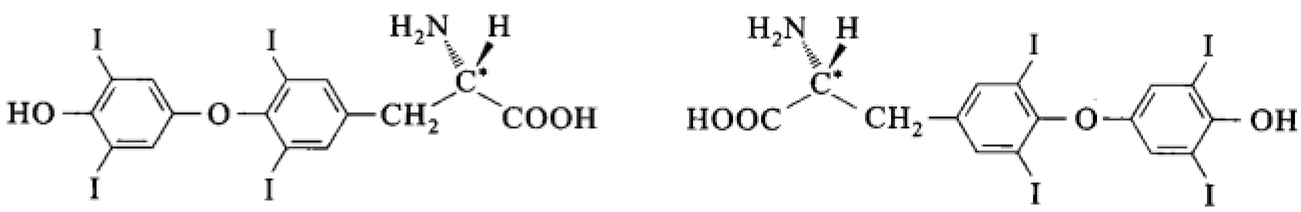
*(i) 

PROBLEM 6-6

In Problem 6-2, you drew the enantiomers for a number of chiral compounds. Now go back and designate each asymmetric carbon atom as either (R) or (S).

6-4 Optical Activity

Mirror-image molecules have nearly identical physical properties. Differences in enantiomers become apparent in their interactions with other chiral molecules, such as enzymes. Still, we need a simple method to distinguish between enantiomers and measure their purity in the laboratory. **Polarimetry** is a common method used to distinguish between enantiomers, based on their ability to rotate the plane of polarized light in opposite directions. For example, the two enantiomers of thyroid hormone are shown below. The (*S*) enantiomer has a powerful effect on the metabolic rate of all the cells in the body. The (*R*) enantiomer is useless. In the laboratory, we distinguish between the enantiomers by observing that the active one rotates the plane of polarized light to the left.



thyroid hormone (*S*) (甲状腺激素)
rotates polarized light to the left

wrong enantiomer (*R*)
rotates polarized light to the right

6-4A Plane-Polarized Light

Most of what we see is unpolarized light, vibrating randomly in all directions. **Plane-polarized light** is composed of waves that vibrate in only one plane. Although there are other types of "polarized light," the term usually refers to plane-polarized light.

When unpolarized light passes through a polarizing filter, the randomly vibrating light waves are filtered so that most of the light passing through is vibrating in one direction (Figure 6-8). The direction of vibration is called the *axis* of the filter. Polarizing filters may be made from carefully cut calcite crystals or from specially treated plastic sheets. Plastic polarizing filters are often used as lenses in sunglasses, because the axis of the filters can be positioned to filter out reflected glare.

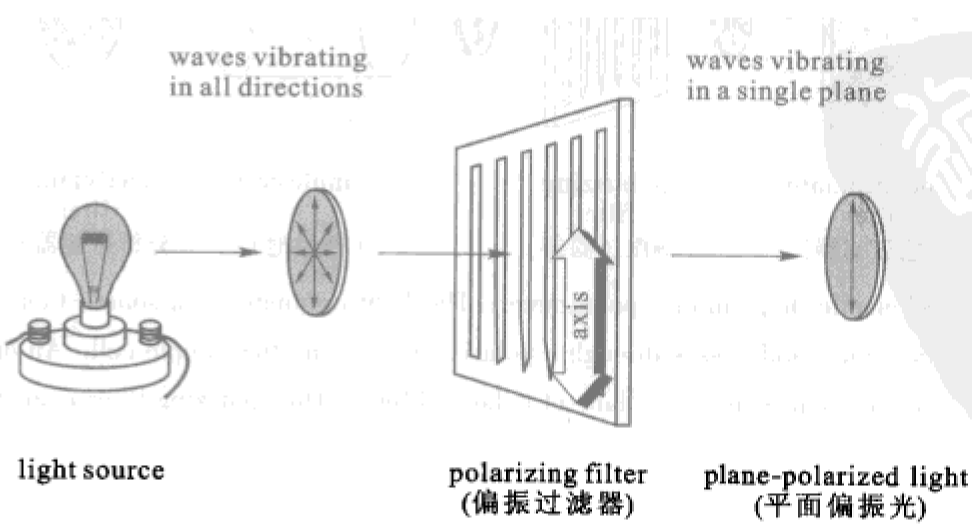


Figure 6-8 Function of a polarizing filter. The waves of plane-polarized light vibrate primarily in a single plane.

6-4B Rotation of Plane-Polarized Light

When polarized light passes through a solution containing a chiral compound, the chiral compound causes the plane of vibration to rotate. Rotation of the plane of polarized light is called **optical activity**, and substances that rotate the plane of polarized light are said to be **optically active.**

Before the relationship between chirality and optical activity was known, enantiomers were called **optical isomers** because they seemed identical except for their opposite optical activity. The term was loosely applied to more than one type of isomerism among optically active compounds, however, and this ambiguous term has been replaced by the well-defined term *enantiomers.*

Two enantiomers have identical physical properties, except for the direction they rotate the plane of polarized light.

Enantiomeric compounds rotate the plane of polarized light by exactly the same amount but in opposite directions.

If the (R) isomer rotates the plane 30° clockwise, the (S) isomer will rotate it 30° counterclockwise. If the (R) enantiomer rotates the plane 5° counterclockwise, the (S) enantiomer will rotate it 5° clockwise.

We cannot predict which direction a particular enantiomer [either (R) or (S)] will rotate the plane of polarized light.

(R) and (S) are simply names, but the direction and magnitude of rotation are physical properties that must be measured.

6-4C Polarimetry

A **polarimeter** measures the rotation of polarized light. It has a tubular cell filled with a solution of the optically active material and a system for passing polarized light through the solution and measuring the rotation as the light emerges (Figure 6-9). The light from a sodium lamp is filtered so that it consists of just one wavelength (one color), because most compounds rotate different wavelengths of light by different amounts. The wavelength of light most commonly used for polarimetry is a yellow emission line in the spectrum of sodium, called the *sodium D line*.

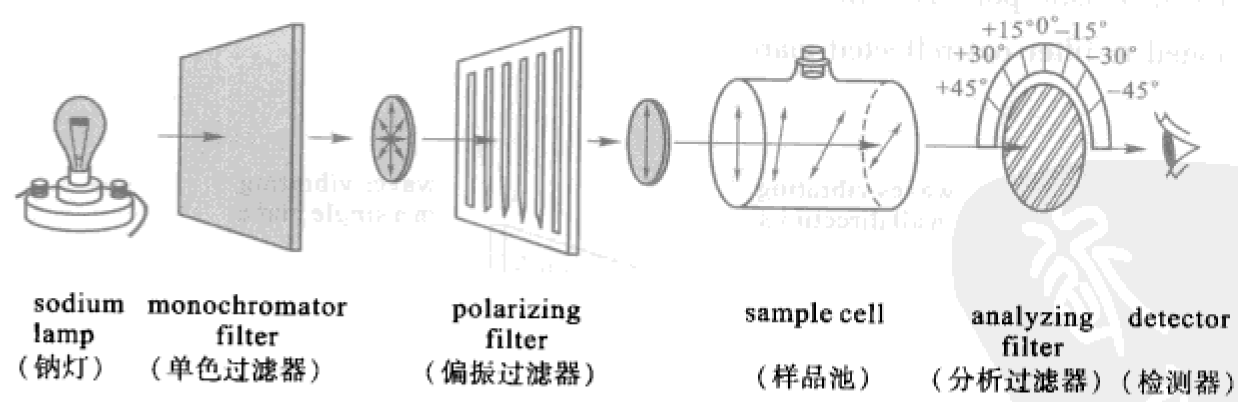


Figure 6-9 Schematic diagram of a polarimeter. The light originates at a source (usually a sodium lamp) and passes through a polarizing filter and the sample cell. An optically active solution rotates the plane of polarized light. The analyzing filter is another polarizing filter equipped with a protractor. It is turned until a maximum amount of light is observed, and the rotation is read from the protractor.

Monochromatic (one color) light from the source passes through a polarizing filter, then through the sample cell containing a solution of the optically active compound. On leaving the sample cell, the polarized light en-

counters another polarizing filter. This filter is movable, with a scale allowing the operator to read the angle between the axis of the second (analyzing) filter and the axis of the first (polarizing) filter. The operator rotates the analyzing filter until the maximum amount of light is transmitted, then the observed rotation is read from the protractor. The observed rotation is symbolized by α, the Greek letter alpha.

Compounds that rotate the plane of polarized light toward the right (clockwise) are called **dextrorotatory**, from the Greek word *dexios*, meaning "toward the right." Compounds that rotate the plane toward the left (counterclockwise) are called **levorotatory**, from the Latin word *laevus*, meaning "toward the left." These terms are sometimes abbreviated by a lowercase *d* or *l*. Using IUPAC notation, the direction of rotation is specified by the (+) or (−) sign of the rotation:

Dextrorotatory (clockwise) rotations are (+).

Levorotatory (counterclockwise) rotations are (−).

For example, the isomer of 2-butanol that rotates the plane of polarized light clockwise is named (+)-2-butanol or *d*-2-butanol. Its enantiomer, (−)-2-butanol or *l*-2-butanol, rotates the plane counterclockwise by exactly the same amount.

6-4D Specific Rotation

The angular rotation of polarized light by a chiral compound is a characteristic physical property of that compound, just like the boiling point or the density. The rotation (α) observed in a polarimeter depends on the concentration of the sample solution and the length of the cell, as well as the optical activity of the compound. For example, twice as concentrated a solution would give twice the original rotation. Similarly, a 20-cm cell gives twice the rotation observed using a similar concentration in a 10-cm cell.

To use the rotation of polarized light as a characteristic property of a compound, we must standardize the conditions for measurement. We define a compound's **specific rotation** $[\alpha]$ as the rotation found using a 10-cm (1-dm) sample cell and a concentration of 1 g/mL. Other cell lengths and concentrations may be used, as long as the observed rotation is divided by the path length of the cell (l) and the mass concentration (ρ).

$$[\alpha] = \frac{\alpha(\text{observed})}{\rho \cdot l}$$

where

α(observed) = rotation observed in the polarimeter

ρ = concentration in grams per mL

l = length of sample cell (path length) in decimeters (dm)

A rotation depends on the wavelength of light used and also on the temperature, so these data are given together with the rotation as $[\alpha]_D^{25}$. Here the "25" means that the measurement was made at 25℃, and the "D" means that the light used was the D line of the sodium spectrum.

If we know that the specific rotation for an enantiomer of 2-butanol is −13.5°, we can predict that the specific rotation of the other enantiomer of 2-butanol will be

$$[\alpha]_D^{25} = +13.5°$$

where the (+) refers to the clockwise direction of the rotation. This enantiomer would be called (+)-2-butanol. We could refer to this pair of enantiomers as (+)-2-butanol and (−)-2-butanol or as (*R*)-2-butanol and (*S*)-2-butanol.

Does this mean that (*R*)-2-butanol is the dextrorotatory isomer because it is named (*R*), and (*S*)-2-butanol is levorotatory because it is named (*S*)? Not at all! The rotation of a compound, (+) or (−), is some-

thing that we measure in the polarimeter, depending on how the molecule interacts with light. The (*R*) and (*S*) nomenclature is our own artificial way of describing how the atoms are arranged in space.

In the laboratory, we can measure a rotation and see whether a particular substance is (+) or (−). On paper, we can determine whether a particular drawing is named (*R*) or (*S*). But it is difficult to predict whether a structure we call (*R*) will rotate polarized light clockwise or counterclockwise. Similarly, it is difficult to predict whether a dextrorotatory substance in a flask has the (*R*) or (*S*) configuration.

PROBLEM 6-7

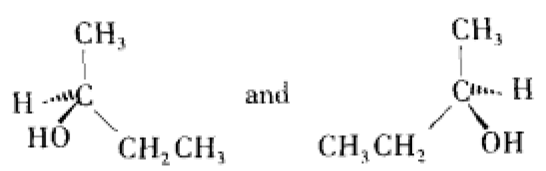
A solution of 2.0 g of (+)-glyceraldehyde, $HOCH_2—CHOH—CHO$, in 10 mL of water was placed in a 100-mm cell. Using the sodium D line, a rotation of +1.74° was found at 25℃. Determine the specific rotation of (+)-glyceraldehyde.

PROBLEM 6-8

A chiral sample gives a rotation that is close to 180°. How can one tell whether this rotation is +180° or −180°?

6-5 Racemic Mixtures

Suppose we had a mixture of equal amounts of (+)-2-butanol and (−)-2-butanol. The (+) isomer would rotate polarized light clockwise with a specific rotation of +13.5°, and the (−) isomer would rotate the polarized light counterclockwise by exactly the same amount. We would observe a rotation of zero, just as though 2-butanol were achiral. A solution of equal amounts of two enantiomers, so that the mixture is optically inactive, is called a **racemic mixture.** Sometimes a racemic mixture is called a **racemate**, a (±) **pair**, or a (***d***, ***l***) **pair.** A racemic mixture is symbolized by placing (±) or (*d*, *l*) in front of the name of the compound. For example, racemic 2-butanol would be symbolized by "(±)-2-butanol" or "(*d*, *l*)-2-butanol."



(*S*)-(+)-2-butanol +13.5° rotation

(*R*)-(−)-2-butanol −13.5° rotation

A racemic mixture contains equal amounts of the two enantiomers

You might think that a racemic mixture would be unusual, since it requires exactly equal amounts of the two enantiomers. This is not the case, however. Many reactions lead to racemic products, especially when an achiral molecule is converted to a chiral molecule.

A reaction that uses optically inactive reactants and catalysts cannot produce a product that is optically active. Any chiral product must be formed as a racemic mixture.

For example, hydrogen adds across the C=O double bond of a ketone to produce an alcohol.

Because the carbonyl group is flat, a simple ketone such as 2-butanone is achiral. Hydrogenation of 2-butanone gives 2-butanol, a chiral molecule (Figure 6-10). This reaction involves adding hydrogen atoms to the C=O carbon atom and oxygen atom. If the hydrogen atoms are added to one face of the double bond, the (*S*) enantiomer results. Addition of hydrogen to the other face forms the (*R*) enantiomer. It is equally probable for hydrogen to add to either face of the double bond, and equal amounts of the (*R*) and (*S*) enantiomers are

formed.

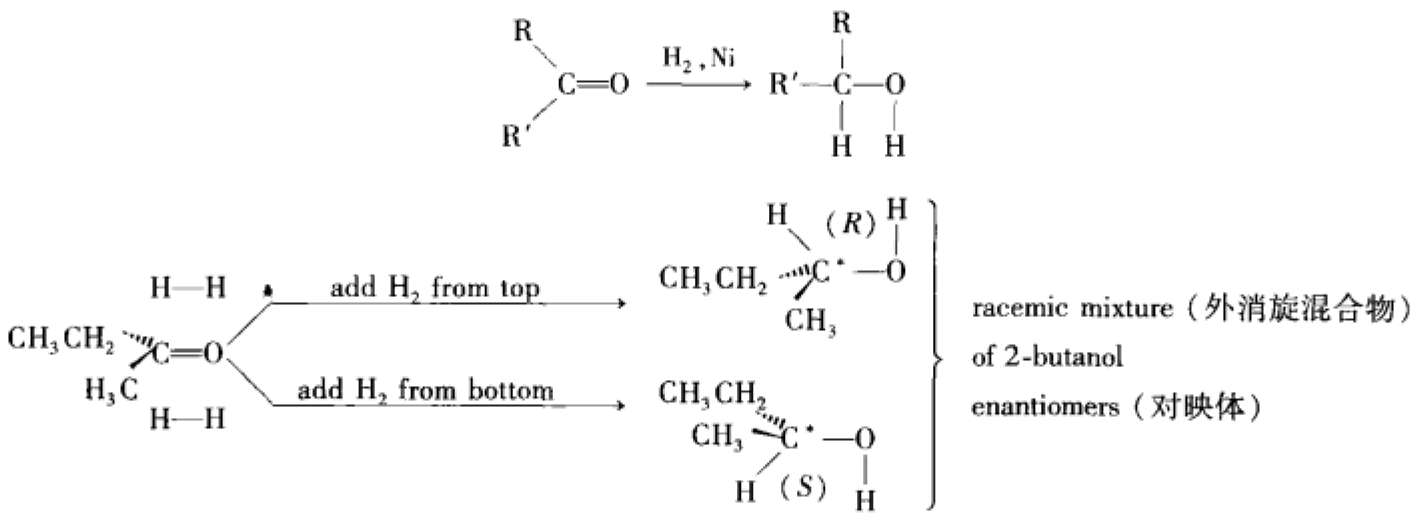


Figure 6-10 Hydrogenation of 2-butanone forms racemic 2-butanol. Hydrogen adds to either face of the double bond. Addition of H_2 to one face gives the (R) product, while addition to the other face gives the (S) product.

Logically, it makes sense that optically inactive reagents and catalysts cannot form optically active products. If the starting materials and reagents are optically inactive, there is no reason for the dextrorotatory product to be favored over a levorotatory one or vice versa. The (+) product and the (−) product are favored equally, and they are formed in equal amounts: a racemic mixture.

6-6 Enantiomeric Excess and Optical Purity

Sometimes we deal with mixtures that are neither optically pure (all one enantiomer) nor racemic (equal amounts of two enantiomers). In these cases, we specify the **optical purity** (**op**) of the mixture. The optical purity of a mixture is defined as the ratio of its rotation to the rotation of a pure enantiomer. For example, if we have some [mostly (+)] 2-butanol with a specific rotation of $+9.72°$, we compare this rotation with the $+13.5°$ rotation of the pure (+) enantiomer.

$$\text{op} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\% = \frac{9.72°}{13.5°} \times 100\% = 72.0\%$$

The **enantiomeric excess** (**ee**) is a similar method for expressing the relative amounts of enantiomers in a mixture. To compute the enantiomeric excess of a mixture, we calculate the *excess* of the predominant enantiomer as a percentage of the entire mixture. For a chemically pure compound, the calculation of enantiomeric excess generally gives the same result as the calculation of optical purity, and we often use the two terms interchangeably. Algebraically, we use the following formula:

$$\text{op} = \text{ee} = \frac{|d-l|}{d+l} \times 100\% = \frac{(\text{excess of one over the other})}{(\text{entire mixture})} \times 100\%$$

The units cancel out in the calculation of either ee or op, so these formulas can be used whether the amounts of the enantiomers are expressed in concentrations, grams, or percentages. For the 2-butanol mixture just described, the optical purity of 72% (+) implies that $d - l = 72\%$, and we know that $d + l = 100\%$. Adding the equations gives $2d = 172\%$. We conclude that the mixture contains 86% of the d or (+) enantiomer and 14% of the l or (−) enantiomer.

SOLVED PROBLEM 6-2

Calculate the e e and the specific rotation of a mixture containing 6 g of (+)-2-butanol and 4 g of (−)-2-butanol.

SOLUTION

In this mixture, there is a 2 g excess of the (+) isomer and a total of 10 g, for an ee of 20%. We can envision this mixture as 80% racemic [4 g (+) and 4 g (−)] and 20% pure (+).

$$\text{op} = \text{ee} = \frac{|6-4|}{6+4} = \frac{2}{10} = 20\%$$

The specific rotation of enantiomerically pure (+)-2-butanol is +13.5°. The rotation of this mixture is

$$\text{observed rotation} = (\text{rotation of pure enantiomer}) \times (\text{op})$$
$$= +13.5° \times 20\% = +2.7°$$

PROBLEM 6−9

When optically pure (*R*)-2-bromobutane is heated with water, 2-butanol is the product. The reaction forms twice as much (*S*)-2-butanol as (*R*)-2-butanol. Calculate the ee and the specific rotation expected for the product.

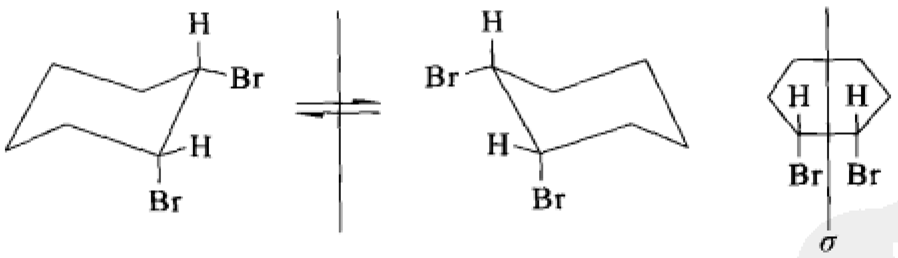
PROBLEM 6−10

A chemist finds that the addition of (+)-epinephrine to the catalytic reduction of 2-butanone (Figure 6−10) gives a product that is slightly optically active, with a specific rotation of +0.45°. Calculate the percentages of (+)-2-butanol and (−)-2-butanol formed in this reaction.

6−7 Chirality of Conformationally Mobile Systems

Let's consider whether *cis*-1,2-dibromocyclohexane is chiral. If we did not know about chair conformations, we might draw a flat cyclohexane ring. With a flat ring, the molecule has an internal mirror plane of symmetry (σ), and it is achiral.

But we know the ring is puckered into a chair conformation with one bromine atom axial and one equatorial. A chair conformation of *cis*-1,2-dibromocyclohexane and its mirror image are shown next. These two mirror-image structures are nonsuperimposable. You may be able to see the difference more easily if you make models of these two conformations.



Does this mean that *cis*-1,2-dibromocyclohexane is chiral? No, it does not, because the chair-chair interconversion is rapid at room temperature. If we had a bottle of just the conformation on the left, the molecules would quickly undergo chair-chair interconversions. Since the two mirror-image conformations interconvert and have identical energies, any sample of *cis*-1,2-dibromocyclohexane must contain equal amounts of the two mirror images.

A molecule cannot be optically active if its chiral conformations are in equilibrium with their mirror images. We consider such a molecule to be achiral.

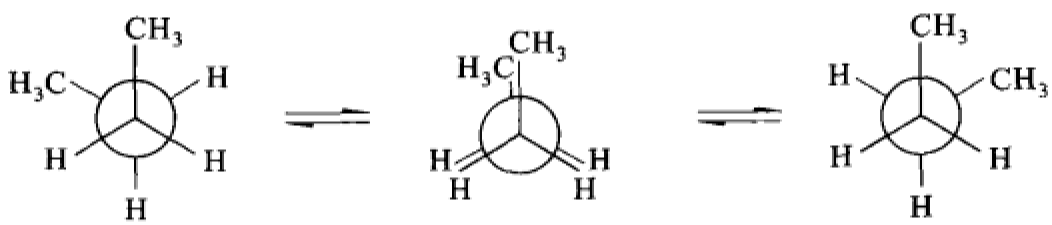
cis-1,2-Dibromocyclohexane appears to exist as a racemic mixture, but with a major difference: It is impossible to create an optically active sample of *cis*-1,2-dibromocyclohexane. The molecule is incapable of showing optical activity. We could have predicted the correct result by imagining that the cyclohexane ring is flat.

This finding leads to a general principle we can use with conformationally mobile systems:

To determine whether a conformationally mobile molecule can be optically active, consider its most symmetric conformation.

An alternative statement of this rule is that a molecule cannot be optically active if it is in equilibrium with a structure (or a conformation) that is achiral. Because conformers differ only by rotations about single bonds, they are generally in equilibrium at room temperature. We can consider cyclohexane rings as though they were flat (the most symmetric conformation), and we should consider straight-chain compounds in their most symmetric conformations (often an eclipsed conformation).

Organic compounds commonly exist as rapidly interconverting chiral conformations. Even ethane is chiral in its skew conformations. When we speak of chirality, however, we intend to focus on observable, persistent properties rather than transient conformations. For example, butane exists in gauche conformations that are chiral, but they quickly interconvert. They are in equilibrium with the totally eclipsed conformation, which is symmetric, implying that butane must be achiral.



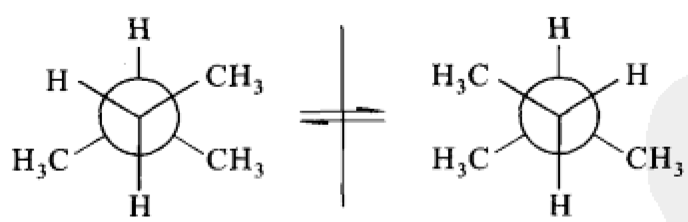
gauche(顺交叉式) (chiral) totally eclipsed(全重叠式) (achiral) gauche (chiral)

SOLVED PROBLEM 6-3

Draw the compound of 2-methylbutane in its most stable conformation(s). Then draw it in its most symmetric conformation, and determine whether it is capable of showing optical activity.

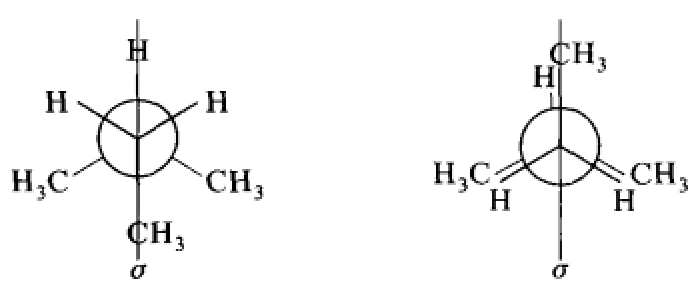
SOLUTION

The most stable conformations of 2-methylbutane are two mirror-image conformations. These conformations are nonsuperimposable, but they can interconvert by rotation around the central bond. So they are not enantiomers.



chiral conformation(手性构象) chiral conformation

2-methylbutane has two symmetric conformations: Either of these conformations is sufficient to show that 2-methylbutane is achiral.



symmetric conformation(对称构象) symmetric conformation

PROBLEM 6-11

1. Make a model of each compound, draw it in its most symmetric conformation, and determine whether it is capable of showing optical activity.
   (a) 1-bromo-1-chloroethane (b) 1-bromo-2-chloroethane
   (c) 1-bromo-1,2-dichloroethane (d) *cis*-1,3-dibromocyclohexane
   (e) *trans*-1,3-dibromocyclohexane (f) *trans*-1,4-dibromocyclohexane
2. Star (*) each asymmetric carbon atom, and compare your result from **1.** with the prediction you would make based on the asymmetric carbons.

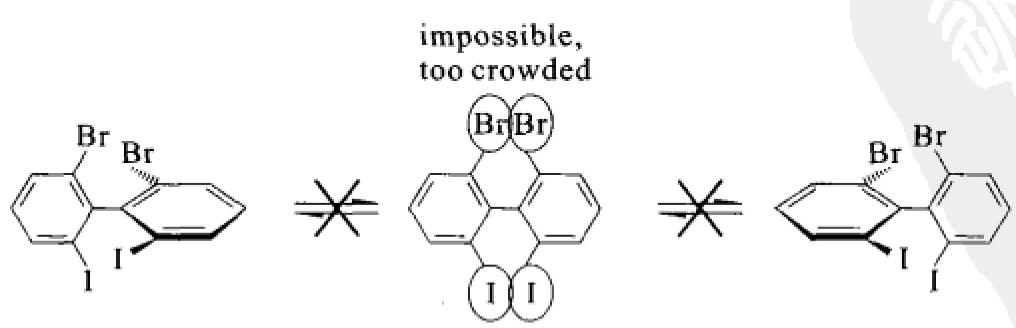
6-8 Chiral Compounds without Asymmetric Atoms

Most chiral organic compounds have at least one asymmetric carbon atom. Some compounds are chiral because they have another asymmetric atom, such as phosphorus, sulfur, or nitrogen, serving as a chirality center. Some compounds are chiral even though they have no asymmetric atoms at all. In these types of compounds, special characteristics of the molecules' shapes lend chirality to the structure.

6-8A Conformational Enantiomerism

Some molecules are so bulky or so highly strained that they cannot easily convert from one chiral conformation to the mirror-image conformation. They cannot achieve the most symmetric conformation because it has too much steric strain or ring strain. Since these molecules are "locked" into a conformation, we must evaluate the individual locked-in conformation to determine whether the molecule is chiral.

Figure 6-11 shows three conformations of a sterically crowded derivative of biphenyl. The center drawing shows the molecule in its most symmetric conformation. This conformation is planar, and it has a mirror plane of symmetry. If the molecule could achieve this conformation, or even pass through it for an instant, it would not be optically active. This planar conformation is very high in energy, however, because the iodine and bromine atoms are too large to be forced so close together. The molecule is *conformationally locked*. It can exist only in one of the two staggered conformations shown on the left and right. These conformations are nonsuperimposable mirror images, and they do not interconvert. They are enantiomers, and they can be separated and isolated. Each of them is optically active, and they have equal and opposite specific rotations.



staggered conformation(交叉构象) (chiral) eclipsed conformation(重叠构象) (symmetric, achiral) staggered conformation (chiral)

Figure 6-11 Three conformations of a biphenyl. This biphenyl cannot pass through its symmetric conformation because there is too much crowding of the iodine and bromine atoms. The molecule is "locked" into one of the two chiral, enantiomeric, staggered conformations.

Even a simple strained molecule can show conformational enantiomerism. *trans*-Cyclooctene is the smallest stable *trans*-cycloalkene, and it is strained. If *trans*-cyclooctene existed as a planar ring, even for an instant, it could not be chiral. Make a molecular model of *trans*-cyclooctene, however, and you will see that it cannot exist as a planar ring. Its ring is folded into the three-dimensional structure pictured in Figure 6-12. The mirror image of this structure is different, and *trans*-cyclooctene is a chiral molecule. In fact, the enantiomers of *trans*-cyclooctene have been separated and characterized, and they are optically active.

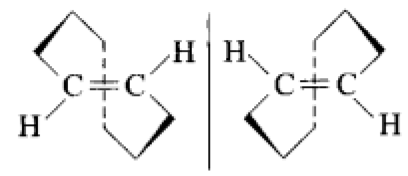


Figure 6-12 Conformational enantiomerism. *trans*-Cyclooctene is strained, unable to achieve a symmetric planar conformation. It is locked into one of these two enantiomeric conformations.

6-8B Allenes

Allenes are compounds that contain the C=C=C unit, with two C=C double bonds meeting at a single carbon atom. The central carbon atom is *sp* hybridized, requiring a linear arrangement of atoms (Section 2-4). The parent compound, propadiene, has the common name *allene*.

sp hybridized

$$H_2C{=}C{=}CH_2$$

allene (丙二烯)

In allene, the central carbon atom is *sp* hybridized and linear, and the two outer carbon atoms are sp^2 hybridized and trigonal. We might imagine that the whole molecule lies in a plane, but this is not correct. The central *sp* hybrid carbon atom must use different *p* orbitals to form the pi bonds with the two outer carbon atoms. The two unhybridized *p* orbitals on the *sp* hybrid carbon atom are perpendicular, so the two pi bonds must also be perpendicular. Figure 6-13 shows the bonding and three-dimensional structure of allene. Allene itself is achiral. If you make a model and its mirror image, you will find it identical with the original molecule. If we add some substituents to allene, however, the molecule may be chiral.

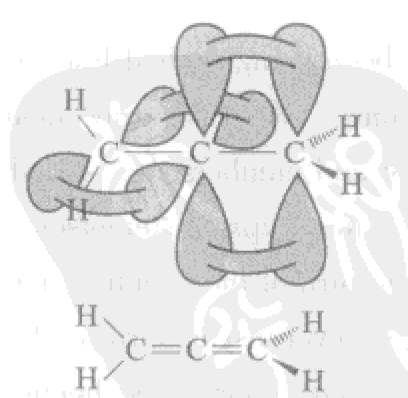


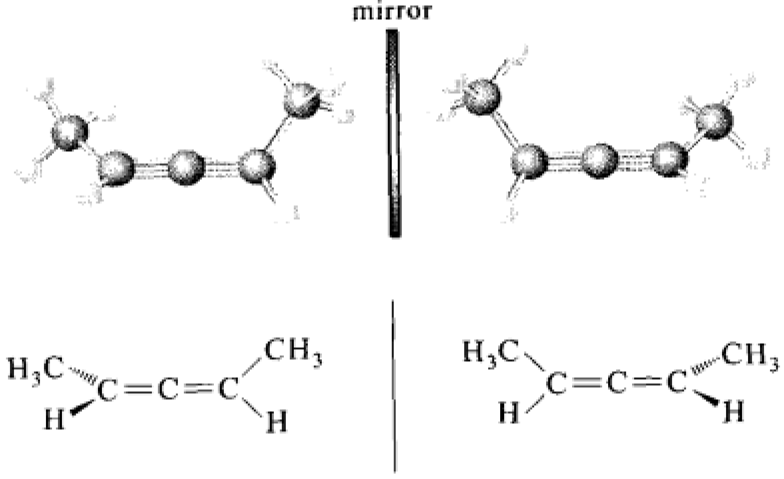
Figure 6-13 Structure of an allene. The two ends of the allene molecule are perpendicular.

Make a model of the following compound:

$$\overset{1}{C}H_3{-}\overset{2}{C}H{=}\overset{3}{C}{=}\overset{4}{C}H{-}\overset{5}{C}H_3$$

2,3-pentadiene (2,3-戊二烯)

Carbon atom 3 is the *sp* hybrid allene carbon atom. Carbons 2 and 4 are both sp^2 and planar, but their planes are perpendicular to each other. None of the carbon atoms is attached to four different atoms, so there is no chiral carbon atom. Nevertheless, 2,3-pentadiene is chiral, as you should see from your models and from the following drawings of the enantiomers.

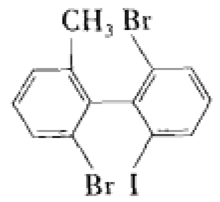


enantiomers of 2,3-pentadiene

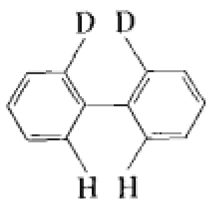
PROBLEM 6-12

Draw three-dimensional representations of the following compounds. Which have asymmetric carbon atoms? Which have no asymmetric carbons but are chiral anyway? Use your models for parts (a) through (d) and any others that seem unclear.

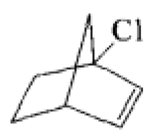
(a) 1,3-dichloropropadiene
(b) 1-chloro-1,2-butadiene
(c) 1-chloro-3-methyl-1,2-butadiene
(d) 1-chloro-1,3-butadiene
(e) bromocyclohexane
(f)



(g)



(h)



6-9 Fischer Projections

We have been using dashed lines and wedges to indicate perspective in drawing the stereochemistry of asymmetric carbon atoms. When we draw molecules with several asymmetric carbons, perspective drawings become time-consuming and cumbersome. In addition, the complicated drawings make it difficult to see the similarities and differences in groups of stereoisomers.

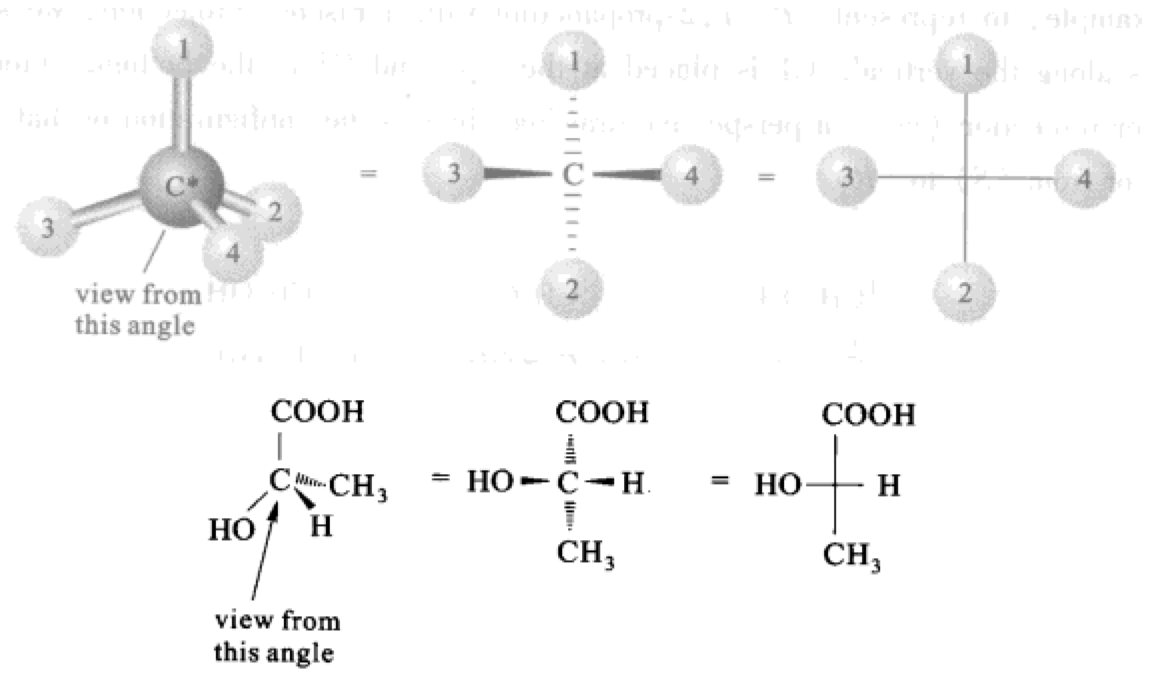
At the turn of the twentieth century, Emil Fischer was studying the stereochemistry of sugars, which contain as many as seven asymmetric carbon atoms. To draw these structures in perspective would have been difficult, and to pick out minor stereochemical differences in the drawings would have been nearly impossible. Fischer developed a symbolic way of drawing asymmetric carbon atoms, allowing them to be drawn rapidly. The **Fischer projection** also facilitates comparison of stereoisomers, holding them in their most symmetric conformation and emphasizing any differences in stereochemistry.

6-9A Drawing Fischer Projections

The Fischer projection looks like a cross, with the asymmetric carbon (usually not drawn in) at the point where the lines cross. The horizontal lines are taken to be wedges—that is, bonds that project out toward the viewer.

The vertical lines are taken to project away from the viewer, as dashed lines. Figure 6–14 shows the perspective implied by the Fischer projection. The center drawing illustrates why this projection is sometimes called the "bow-tie convention".

Fischer projections that differ by a 180° rotation are the same. When we rotate a Fischer projection by 180°, the vertical (dashed line) bonds still end up vertical, and the horizontal (wedged) lines still end up horizontal. The "horizontal lines forward, vertical lines back" convention is maintained.

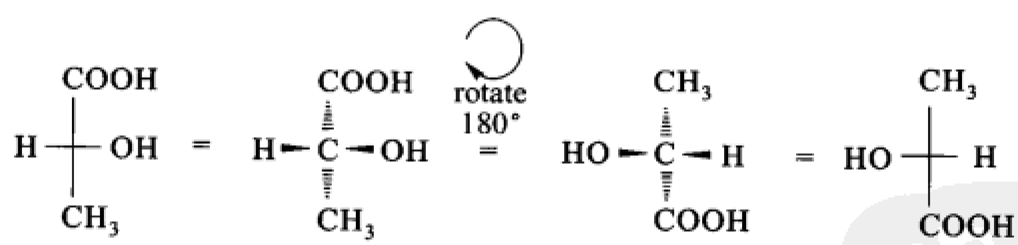


(*S*)-lactic acid [(*S*)-乳酸]
perspective drawing (透视图)

(*S*)-lactic acid
Fischer projection (费歇尔投影式)

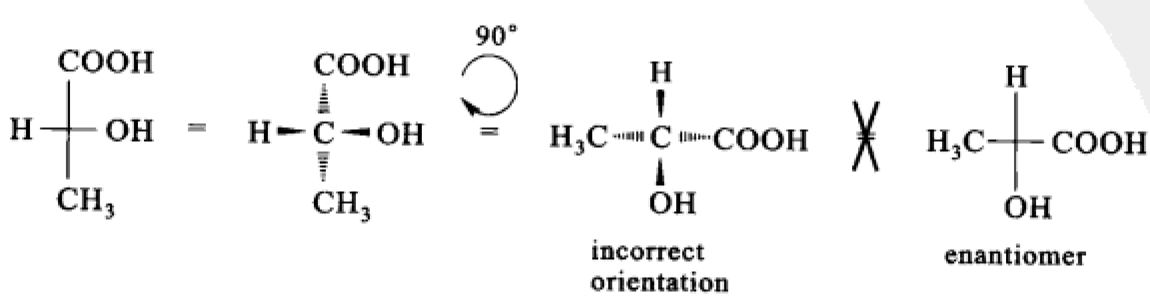
Figure 6–14 Perspective in a Fischer projection. The Fischer projection uses a cross to represent an asymmetric carbon atom. The horizontal lines project toward the viewer, and the vertical lines project away from the viewer.

Rotation by 180° is allowed.



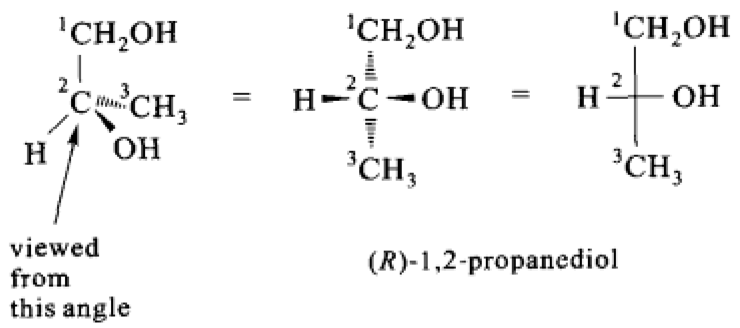
On the other hand, if we were to rotate a Fischer projection by 90°, we would change the configuration and confuse the viewer. The original projection has the vertical groups back (dashed lines) and the horizontal groups forward. When we rotate the projection by 90°, the vertical bonds become horizontal and the horizontal bonds become vertical. The viewer assumes that the horizontal bonds come forward and that the vertical bonds go back. The viewer sees a different molecule (actually, the enantiomer of the original molecule).

A 90° rotation is NOT allowed.



In comparing Fischer projections, we cannot rotate them by 90° and we cannot flip them over. Either of these operations gives an incorrect representation of the molecule. The Fischer projection must be kept in the plane of the paper, and it may be rotated only by 180°.

The final rule for drawing Fischer projections helps to ensure that we do not rotate the drawing by 90°. This rule is that the carbon chain is drawn along the vertical line of the Fischer projection, usually with the IUPAC numbering from top to bottom. In most cases, this numbering places the most highly oxidized carbon substituent at the top. For example, to represent (R)-1,2-propanediol with a Fischer projection, we should arrange the three carbon atoms along the vertical. C1 is placed at the top, and C3 at the bottom. Interchanging any two groups on a Fischer projection (or on a perspective drawing) inverts the configuration of that asymmetric carbon from (R) to (S) or from (S) to (R)



(R)-1,2-propanediol

PROBLEM 6-13

Draw a Fischer projection for each compound. Remember that the cross represents an asymmetric carbon atom, and the carbon chain should be along the vertical, with the IUPAC numbering from top to bottom.

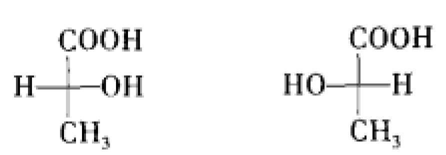
(a) (S)-1,2-propanediol **(b)** (R)-2-bromo-1-butanol

(c) (S)-1,2-dibromobutane **(d)** (R)-2-butanol

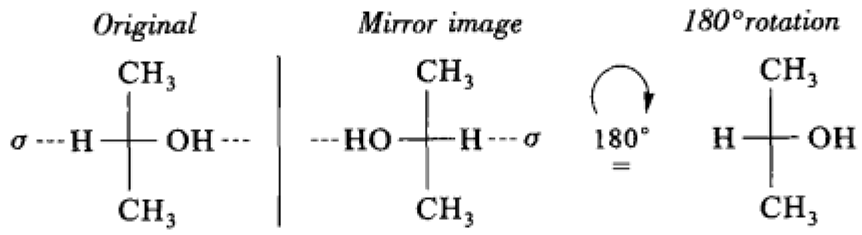
(e) (R)-glyceraldehyde, $HO{-}^{3}CH_2{-}^{2}CH(OH){-}^{1}CHO$

6-9B Drawing Mirror Images of Fischer Projections

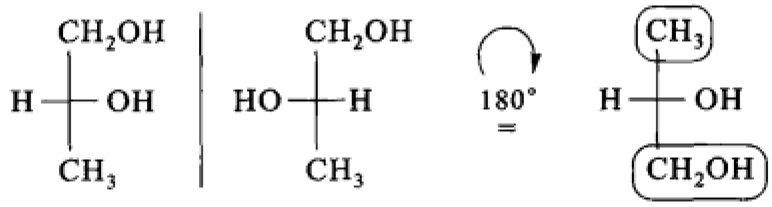
How does one draw the mirror image of a molecule drawn in Fischer projection? With our perspective drawings, the rule was to reverse left and right while keeping the other directions (up and down, front and back) in their same positions. This rule still applies to Fischer projections. Interchanging the groups on the horizontal part of the cross reverses left and right while leaving the other directions unchanged.


(R)-lactic acid (S)-lactic acid

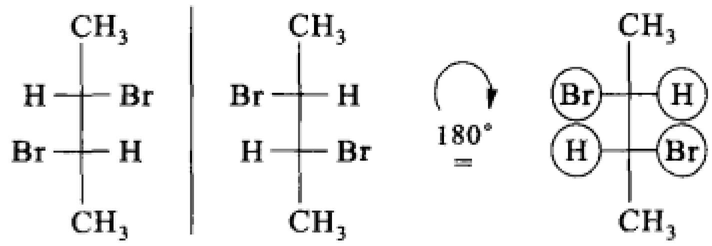
Testing for enantiomerism is particularly simple using Fischer projections. If the Fischer projections are properly drawn (carbon chain along the vertical), and if the mirror image cannot be made to look the same as the original structure with a 180° rotation in the plane of the paper, the two mirror images are enantiomers. In the following examples, any groups that fail to superimpose after a 180° rotation are circled.

2-propanol 

These mirror images are the same. 2-Propanol is achiral.

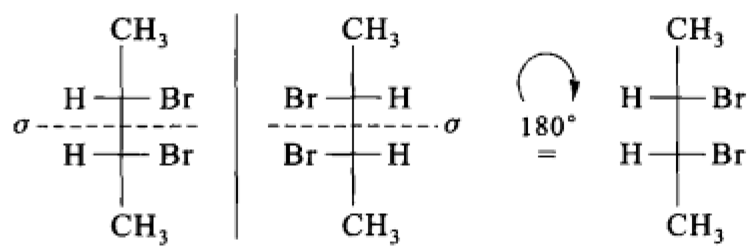
(*R*)-1,2-propanediol 

These mirror images are different. 1,2-Propanediol is chiral.

(2*S*,3*S*)-2,3-dibromobutane 

These mirror images are different. This structure is chiral.

Mirror planes of symmetry are particularly easy to identify from the Fischer projection because this projection is normally the most symmetric conformation. In the first preceding example and in the following example, the symmetry planes are indicated in red; these molecules with symmetry planes cannot be chiral.

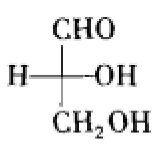
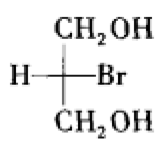
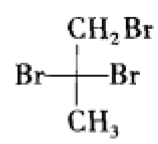
(2*S*, 3*R*)-2, 3-dibromobutane 

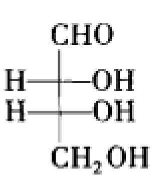
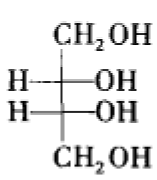
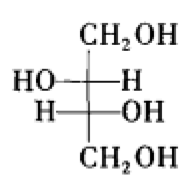
These mirror images are the same. This structure is achiral.

PROBLEM 6-14

For each Fischer projection

1. Draw the mirror image.
2. Determine whether the mirror image is the same as, or different from, the original structure.
3. Draw in any mirror planes of symmetry that are apparent from the Fischer projections.

(a)  (b)  (c) 

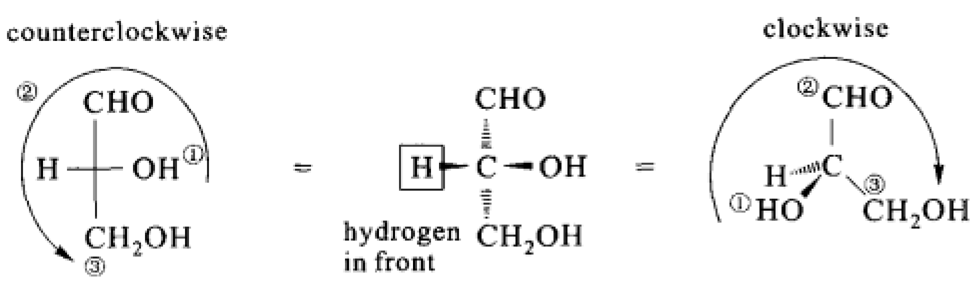
(d)  (e)  (f) 

6-9C Assigning (*R*) and (*S*) Configurations from Fischer Projections

The Cahn-Ingold-Prelog convention (Section 3-5C) can be applied to structures drawn using Fischer projections. Let's review the two rules for assigning (*R*) and (*S*): (1) Assign priorities to the groups bonded to the asymmetric carbon atom; (2) put the lowest-priority group (usually H) in back, and draw an arrow from group 1 to group 2 to group 3. Clockwise is (*R*), and counterclockwise is (*S*).

The (*R*) or (*S*) configuration can also be determined directly from the Fischer projection, without having to convert it to a perspective drawing. The lowest-priority atom is usually hydrogen. In the Fischer projection, the carbon chain is along the vertical line, so the hydrogen atom is on the horizontal line and projects out in front. Once we have assigned priorities, we can draw an arrow from group 1 to group 2 to group 3 and see which way it goes. If the molecule were turned around so that the hydrogen would be in back [as in the definition of (*R*) and (*S*)], the arrow would rotate in the other direction. By mentally turning the arrow around, we can assign the configuration.

As an example, consider the Fischer projection formula of one of the enantiomers of glyceraldehyde. First priority goes to the —OH group, followed by the —CHO group and the —CH_2OH group. The hydrogen atom receives the lowest priority. The arrow from group 1 to group 2 to group 3 appears counterclockwise in the Fischer projection. If the molecule is turned over so the hydrogen is in back, the arrow is clockwise, so this is the (*R*) enantiomer of glyceraldehyde.



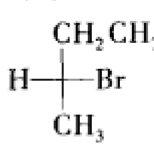
Fischer projection
(*R*)-(+)-glyceraldehyde [(*R*)-(+)-甘油醛]

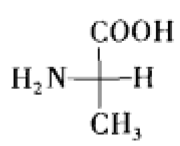
perspective drawing
(*R*)-(+)-glyceraldehyde

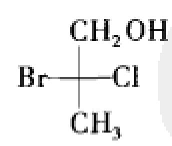
PROBLEM 6-15

For each Fischer projection, label each asymmetric carbon atom as (*R*) or (*S*).

(a)-(f) the structures in Problem 6-14

(g) 

(h) 

(i) 

(careful-no hydrogen)

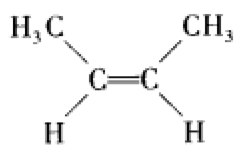
6-10 Diastereomers

We have defined *stereoisomers* as isomers whose atoms are bonded together in the same order but differ in how the atoms are directed in space. We have also considered enantiomers (mirror-image isomers) in detail. All other stereoisomers are classified as **diastereomers**, which are defined as *stereoisomers that are not mirror images.*

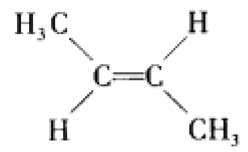
Most diastereomers are either geometric isomers or compounds containing two or more chirality centers (usually asymmetric carbons).

6-10A cis-trans Isomerism on Double Bonds

We have already seen one class of diastereomers, the **cis-trans isomers**, or **geometric isomers.** For example, there are two isomers of 2-butene:



cis-2-butene

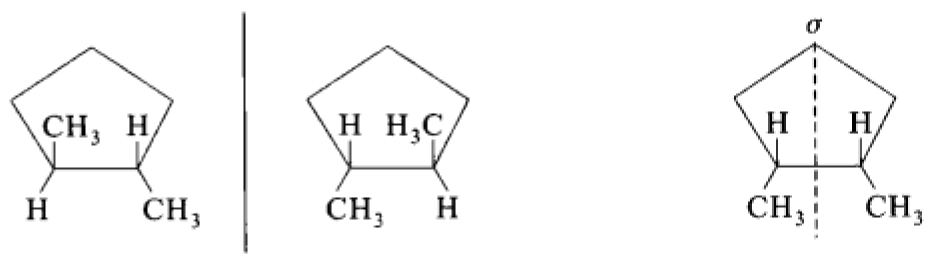


trans-2-butene

These stereoisomers are not mirror images of each other, so they are not enantiomers. They are diastereomers.

6-10B cis-trans Isomerism on Rings

cis-trans Isomerism is also possible when there is a ring present. *cis*-and *trans*-1,2-Dimethylcyclopentane are geometric isomers, and they are also diastereomers. The trans diastereomer has an enantiomer, but the cis diastereomer has an internal mirror plane of symmetry, so it is achiral.

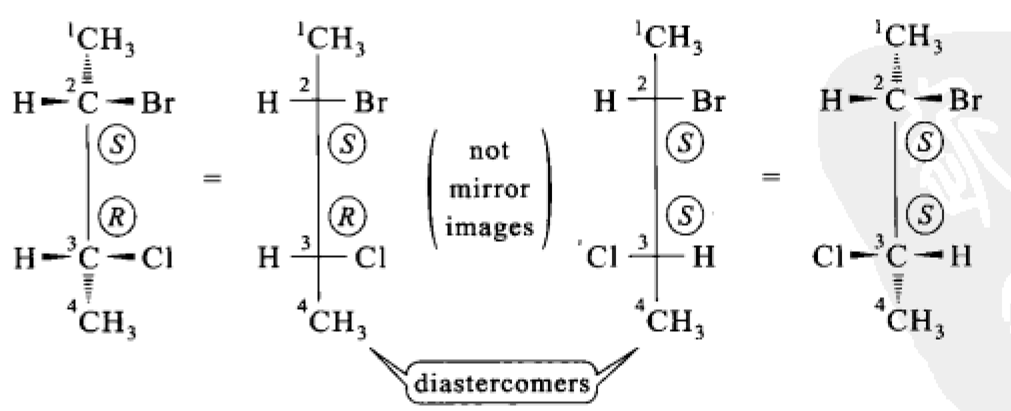


enantiomers of *trans*-1,2-dimethylcyclopentane　　*cis*-1,2-dimethylcyclopentane(achiral)

diastereomers (非对映体)

6-10C Diastereomers of Molecules with Two or More Chirality Centers

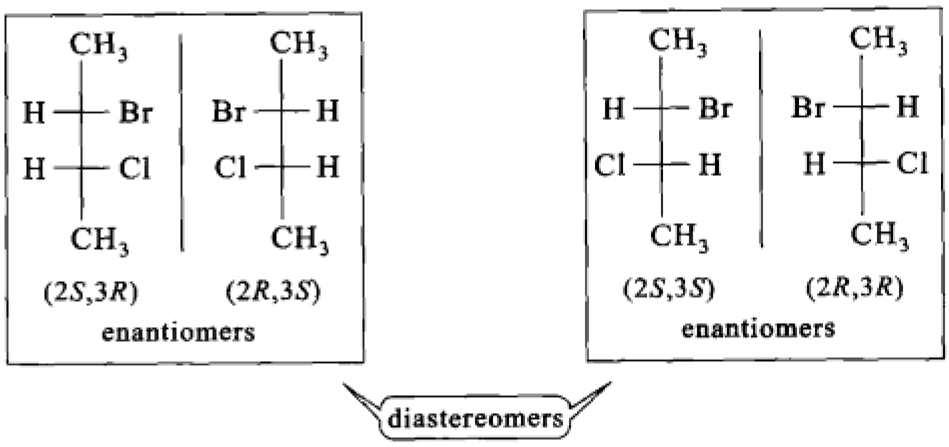
Apart from geometric isomers, most other compounds that show diastereomerism have two or more chirality centers, usually asymmetric carbon atoms. For example, 2-bromo-3-chlorobutane has two asymmetric carbon atoms, and it exists in two diastereomeric forms. Make molecular models of these two stereoisomers.



These two structures are not the same; they are stereoisomers because they differ in the orientation of their atoms in space. They are not enantiomers, however, because they are not mirror images of each other: C2 has the (S) configuration in both structures, while C3 is (R) in the structure on the left and (S) in the stucture on the right. The C3 carbon atoms are mirror images of each other, but the C2 carbon atoms are not. If these two

compounds were mirror images of each other, both asymmetric carbons would have to be mirror images of each other.

Since these compounds are stereoisomers but not enantiomers, they must be diastereomers. In fact, both of these diastereomers are chiral and each has an enantiomer. Thus, there are a total of four stereoisomeric 2-bromo-3-chlorobutanes: two pairs of enantiomers. Either member of one pair of enantiomers is a diastereomer of either member of the other pair.

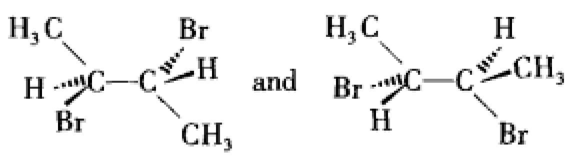


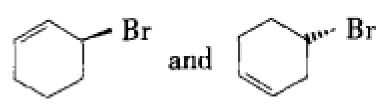
PROBLEM 6–16

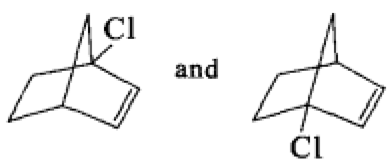
For each pair, give the relationship between the two compounds. Making models will be helpful.

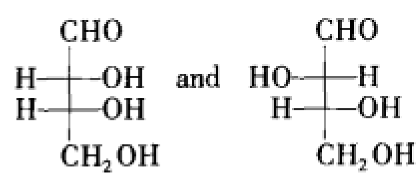
(a) (2*R*, 3*S*)-2, 3-dibromohexane and (2*S*, 3*R*)-2, 3-dibromohexane

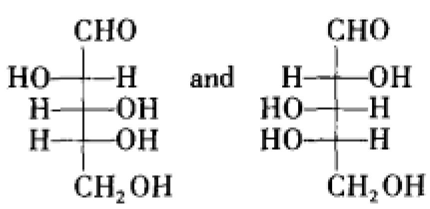
(b) (2*R*, 3*S*)-2, 3-dibromohexane and (2*R*, 3*R*)-2, 3-dibromohexane

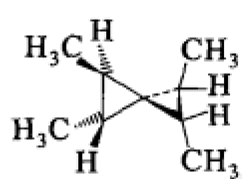
(c) 

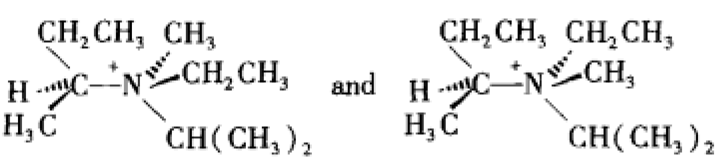
(d) 

(e) 

(f) 

(g) 

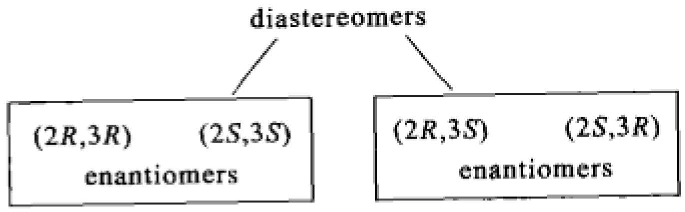
*(h)  and its mirror image

(i) 

6–11 Stereochemistry of Molecules with Two or More Asymmetric Carbons

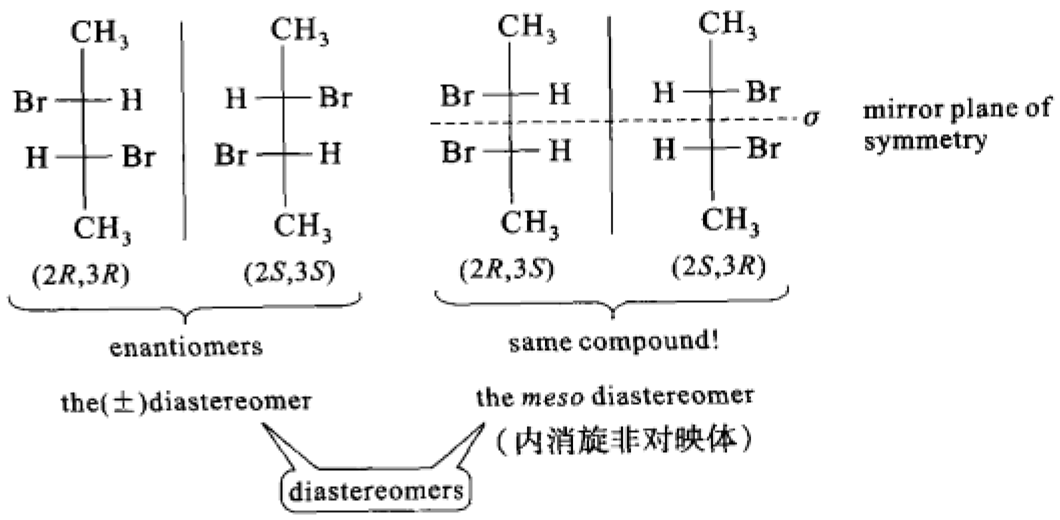
In the preceding section, we saw there are four stereoisomers (two pairs of enantiomers) of 2-bromo-3-chlorobutane. These four isomers are simply all the permutations of (*R*) and (*S*) configurations at the two asymmetric

carbon atoms, C2 and C3:



A compound with n asymmetric carbon atoms often has 2^n stereoisomers. This formula is called the **2^n rule**, where n is the number of chirality centers (usually asymmetric carbon atoms). The 2^n rule suggests we should look for a *maximum* of 2^n stereoisomers. We may not always find 2^n isomers, especially when two of the asymmetric carbon atoms have identical substituents.

2, 3-Dibromobutane has fewer than 2^n stereoisomers. It has two asymmetric carbons (C2 and C3), so the 2^n rule predicts a maximum of four stereoisomers. The four permutations of (R) and (S) configurations at C2 and C3 are shown next. Make molecular models of these structures to compare them.



There are only three stereoisomers of 2,3-dibromobutane because two of the four structures are identical. The diastereomer on the right is achiral, having a mirror plane of symmetry. The asymmetric carbon atoms have identical substituents, and the one with (R) configuration reflects into the other having (S) configuration. It seems almost as though the molecule were a racemic mixture within itself.

6-12 Meso Compounds

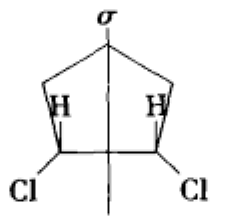
Compounds that are achiral even though they have asymmetric carbon atoms are called **meso compounds.** The ($2R$, $3S$) isomer of 2,3-dibromobutane is a meso compound; most meso compounds have this kind of symmetric structure, with two similar halves of the molecule having opposite configurations. In speaking of the two diastereomers of 2,3-dibromobutane, the symmetric one is called the *meso diastereomer*, and the chiral one is called the (±) *diastereomer*, since one enantiomer is (+) and the other is (−).

MESO COMPOUND: An achiral compound that has chirality centers.

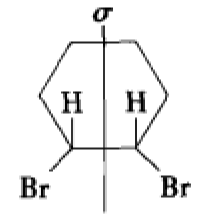
The term *meso* (Greek, "middle") was used to describe an achiral member of a set of diastereomers, some of which are chiral. The optically inactive isomer seemed to be in the "middle" between the dextrorotatory and levorotatory isomers. The definition just given ("an achiral compound with chirality centers") is more easily applied, especially when you remember that chirality centers are usually asymmetric carbon atoms.

We have already seen other meso compounds, although we have not yet called them that. For example, the cis isomer of 1, 2-dichlorocyclopentane has two asymmetric carbon atoms, yet it is achiral. Thus it is a meso

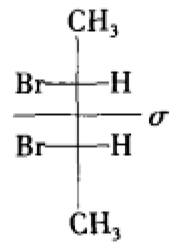
compound. *cis*-1,2-Dibromocyclohexane is not symmetric in its chair conformation, but it consists of equal amounts of two enantiomeric chair conformations in a rapid equilibrum. We are justified in looking at the molecule in its symmetric flat conformation to show that it is achiral and meso. For acyclic compounds, the Fischer projection helps to show the symmetry of meso compounds.



cis-1, 2-dichlorocyclopentane

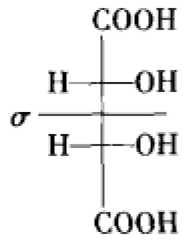


cis-1, 2-dibromocyclohexane



meso-2, 3-dibromobutane

（内消旋-2, 3-二溴丁烷）



meso-tartaric acid

（内消旋酒石酸）

SOLVED PROBLEM 6-4

One source defines a meso compound as "an achiral compound with stereocenters." Why is this a poor definition?

SOLUTION

A stereocenter is an atom at which the interchange of two groups gives a stereoisomer. Stereocenters include both chirality centers and double-bonded carbons giving rise to cis-trans isomers. For example, the isomers of 2-butene are achiral and they contain stereocenters (circled), so they would meet this definition. They have no chiral diastereomers, however, so they are not correctly called meso.

PROBLEM 6-17

Which of the following compounds are chiral? Draw each compound in its most symmetric conformation, star(*) any asymmetric carbon atoms, and draw in any mirror planes. Label any meso compounds. You may use Fischer projections if you prefer.

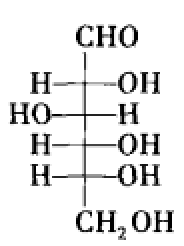
(a) *meso*-2, 3-dibromo-2, 3-dichlorobutane

(b) (±)-2, 3-dibromo-2, 3-dichlorobutane

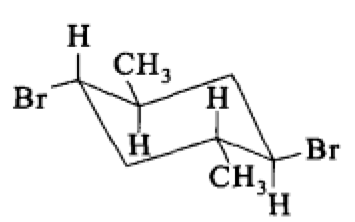
(c) butane

(d) (2*R*, 3*S*) $\overset{4}{\text{HOCH}_2}-\overset{3}{\text{CHBr}}-\overset{2}{\text{CHOH}}-\overset{1}{\text{CH}_2\text{OH}}$

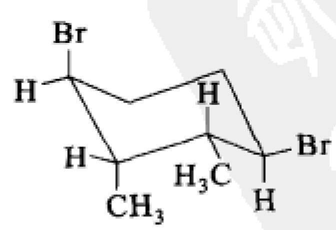
(e)



(f)



(g)



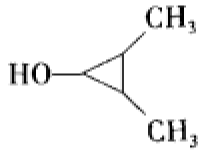
PROBLEM 6-18

Draw all the distinct stereoisomers for each structure. Show the relationships (enantiomers, diastereomers, etc.) between the isomers. Label any meso isomers, and draw in any mirror planes of symmetry.

(**a**) $CH_3—CHCl—CHOH—COOH$

(**b**) tartaric acid, $HOOC—CHOH—CHOH—COOH$

(**c**) $HOOC—CHBr—CHOH—CHOH—COOH$

(**d**) 

6−13 Absolute and Relative Configuration

Throughout our study of stereochemistry, we have drawn three-dimensional representations, and we have spoken of asymmetric carbons having the (R) or (S) configuration. These ways of describing the configuration of a chirality center are *absolute*; that is, they give the actual orientation of the atoms in space. We say that these methods specify the **absolute configuration** of the molecule. For example, given the name "(R)-2-butanol," any chemist can construct an accurate molecular model or draw a three-dimensional representation.

ABSOLUTE CONFIGURATION: The detailed stereochemical picture of a molecule, including how the atoms are arranged in space. Alternatively, the (R) or (S) configuration at each chirality center.

Chemists have determined the absolute configurations of many chiral compounds since 1951, when X-ray crystallography was first used to find the orientation of atoms in space. Before 1951, there was no way to link the stereochemical drawings with the actual enantiomers and their observed rotations. No absolute configurations were known. It was possible, however, to correlate the configuration of one compound with another and to show that two compounds had the same or opposite configurations. When we convert one compound into another using a reaction that does not break bonds at the asymmetric carbon atom, we know that the product must have the same **relative configuration** as the reactant, even if we cannot determine the absolute configuration of either compound.

RELATIVE CONFIGURATION: The experimentally determined relationship between the configurations of two molecules, even though we may not know the absolute configuration of either.

For example, optically active 2-methyl-1-butanol reacts with PBr_3 to give optically active 1-bromo-2-methylbutane. None of the bonds to the asymmetric carbon atom are broken in this reaction, so the product must have the same configuration at the asymmetric carbon as the starting material does.

$$CH_3CH_2\overset{*}{C}H(CH_3)CH_2OH + PBr_3 \longrightarrow CH_3CH_2\overset{*}{C}H(CH_3)CH_2Br$$

(+)-2-methyl-1-butanol, $[\alpha]_D^{25} = +5.8°$ → (−)-1-bromo-2-methylbutane, $[\alpha]_D^{25} = -4.0°$

We say that (+)-2-methyl-1-butanol and (−)-1-bromo-2-methylbutane have the same relative configuration, even though we don't have the foggiest idea whether either of these is (R) or (S) unless we relate them to a compound whose absolute configuration has been established by X-ray crystallography.

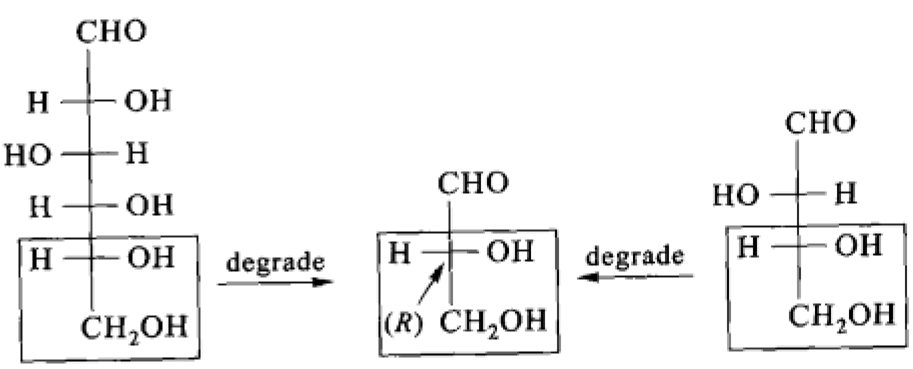
Before the advent of X-ray crystallography, several systems were used to compare the relative configurations of chiral compounds with those of standard compounds. Only one of these systems is still in common use today: the **D-L system**, also known as the *Fischer-Rosanoff convention*. The configurations of sugars and amino acids were related to the enantiomers of glyceraldehyde. Compounds with the same relative configuration as (+)-glyc-

eraldehyde were assigned the D prefix, and those with the relative configuration of (−)-glyceraldehyde were given the L prefix.

L-(−)-glyceraldehyde [L-(−)-甘油醛] | an L-amino acid (L-氨基酸) | L-(−)-serine [L-(−)-丝氨酸] | L-(+)-glutamic acid [L-(+)-谷氨酸]

We now know the absolute configurations of the glyceraldehyde enantiomers: The (+) enantiomer has the (*R*) configuration, with the hydroxyl (OH) group on the right in the Fischer projection. The (−) enantiomer has the (*S*) configuration, with the hydroxyl group on the left. Most naturally occurring amino acids have the L configuration, with the amino (NH_2) group on the left in the Fischer projection.

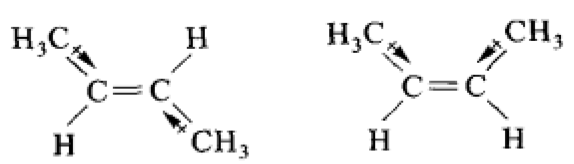
Sugars have several asymmetric carbons, but they can all be degraded to glyceraldehyde by oxidizing them from the aldehyde end. Most naturally occurring sugars degrade to (+)-glyceraldehyde, so they are given the D prefix. This means that the bottom asymmetric carbon of the sugar has its hydroxyl (OH) group on the right in the Fischer projection.



D-(+)-glucose [D-(+)-葡萄糖] | D-(+)-glyceraldehyde [D-(+)-甘油醛] | D-(−)-threose [D-(−)-苏糖]

6−14 Physical Properties of Diastereomers

We have seen that enantiomers have identical physical properties except for the direction in which they rotate polarized light. Diastereomers, on the other hand, generally have different physical properties. For example, consider the diastereomers of 2-butene (shown next). The symmetry of *trans*-2-butene causes the dipole moments of the bonds to cancel. The dipole moments in *cis*-2-butene do not cancel but add together to create a molecular dipole moment. The dipole-dipole attractions of *cis*-2-butene give it a higher boiling point than *trans*-2-butene.

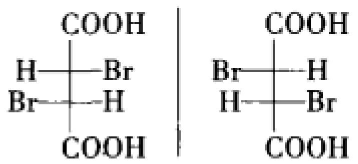


μ=0
trans-2-butene
bond dipoles cancel
bp=0.9℃

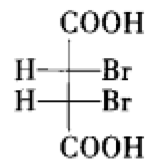
μ=0.33 D
cis-2-butene
vector sum dipole
bp=3.7℃

Diastereomers that are not geometric isomers also have different physical properties. The two diastereomers

of 2,3-dibromosuccinic acid have melting points that differ by nearly 100℃!

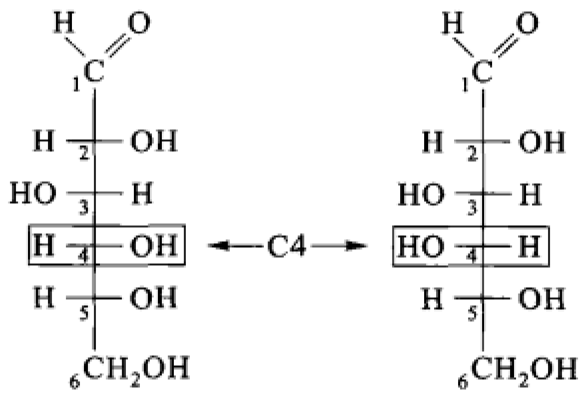


(+) and (-)-2,3-dibromosuccinic acid
mp for either is 158℃
[(+)和(-)-2, 3-二溴丁二酸]



meso-2,3-dibromosuccinic acid
mp 256℃
(内消旋-2, 3-二溴丁二酸)

Most of the common sugars are diastereomers of glucose. All these diastereomers have different physical properties. For example, glucose and galactose are diastereomeric sugars that differ only in the stereochemistry of one asymmetric carbon atom, C4.



D-(+)-glucose, mp 148 ℃ D-(+)-galactose, mp 167 ℃
[D-(+)-葡萄糖] [D-(+)-半乳糖]

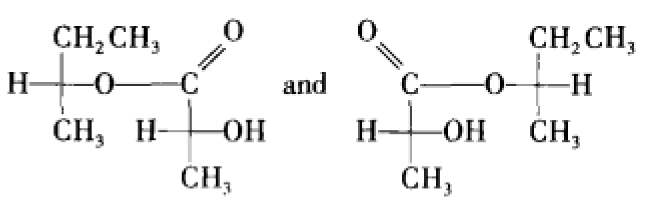
Because diastereomers have different physical properties, we can separate them by ordinary means such as distillation, recrystallization, and chromatography. As we will see in the next section, the separation of enantiomers is a more difficult process.

PROBLEM 6-19

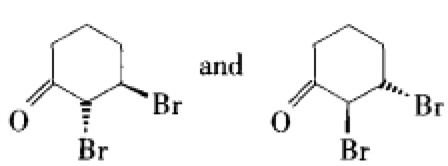
Which of the following pairs of compounds could be separated by recrystallization or distillation?

(a) *meso*-tartaric acid and (±)-tartaric acid (HOOC—CHOH—CHOH—COOH)

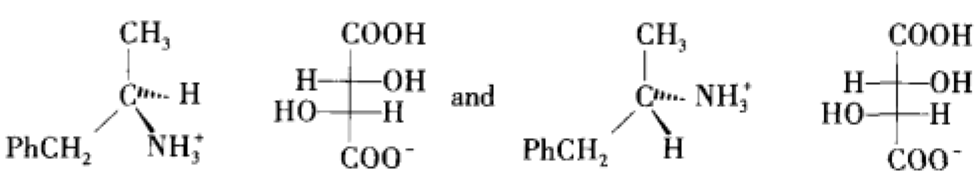
(b)



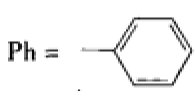
(c)



***(d)**

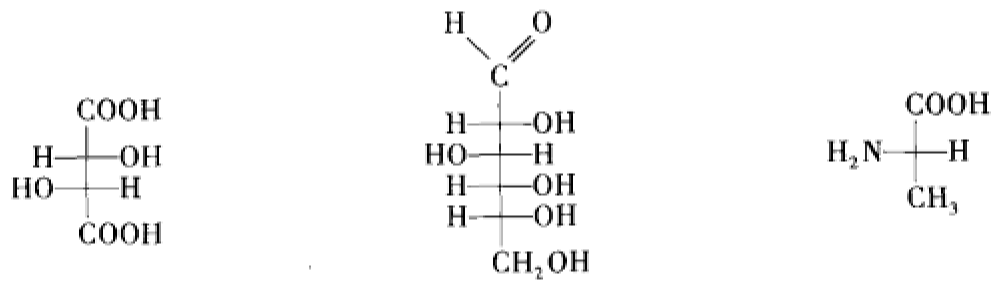


(an acid-base salt)



6−15 Resolution of Enantiomers

Pure enantiomers of optically active compounds are often obtained by isolation from biological sources. Most optically active molecules are found as only one enantiomer in living organisms. For example, pure (+)-tartaric acid can be isolated from the precipitate formed by yeast during the fermentation of wine. Pure (+)-glucose is obtained from many different sugar sources, such as grapes, sugar beets, sugarcane, and honey. Alanine is a common amino acid found in protein as the pure (+) enantiomer.

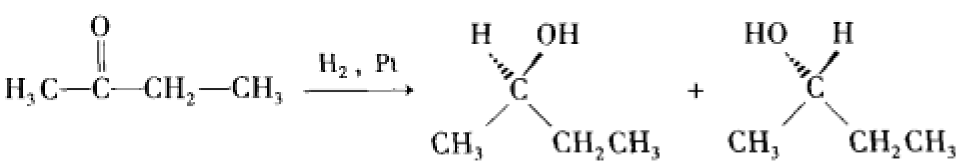


L-(+)-tartaric acid
(2R, 3R)-tartaric acid
[(2R, 3R)－酒石酸]

D-(+)-glucose
[D－(+)－葡萄糖]

L-(+)-alanine
[L－(+)－丙氨酸]

When a chiral compound is synthesized from achiral reagents, however, a racemic mixture of enantiomers is obtained. For example, we saw that the reduction of 2-butanone (achiral) to 2-butanol (chiral) gives a racemic mixture:



2-butanone　　(R)-2-butanol　　(S)-2-butanol

If we need one pure enantiomer of 2-butanol, we must find a way of separating it from the other enantiomer. The separation of enantiomers is called **resolution**, and it is a different process from the usual physical separations. A chiral probe is necessary for the resolution of enantiomers; such a chiral compound or apparatus is called a **resolving agent.**

In 1848, Louis Pasteur noticed that a salt of racemic (±)-tartaric acid crystallizes into mirror-image crystals. Using a microscope and a pair of tweezers, he physically separated the enantiomeric crystals. He found that solutions made from the "left-handed" crystals rotate polarized light in one direction and solutions made from the "right-handed" crystals rotate polarized light in the opposite direction. Pasteur had accomplished the first artificial resolution of enantiomers. Unfortunately, few racemic compounds crystallize as separate enantiomers, and other methods of separation are required.

6−15A Chemical Resolution of Enantiomers

The traditional method for resolving a racemic mixture into its enantiomers is to use an enantiomerically pure natural product that bonds with the compound to be resolved. When the enantiomers of the racemic compound bond to the pure resolving agent, a pair of diastereomers results. The diastereomers are separated, then the resolving agent is cleaved from the separated enantiomers.

Let's consider how we might resolve a racemic mixture of (R)-and (S)-2-butanol. We need a resolving agent that reacts with an alcohol and that is readily available in an enantiomerically pure state. A carboxylic acid combines with an alcohol to form an ester. Although we have not yet studied the chemistry of esters (Chapter

22), the following equation shows how an acid and an alcohol can combine with the loss of water:

$$\underset{\text{acid}}{\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH}} + \underset{\text{alcohol}}{\mathrm{R'{-}OH}} \xrightleftharpoons{(\mathrm{H^+\ catalyst})} \underset{\text{ester}}{\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}R'}} + \underset{\text{water}}{\mathrm{H{-}O{-}H}}$$

For our resolving agent, we need an optically active chiral acid to react with 2-butanol. Any winery can provide large amounts of pure (+)-tartaric acid. Figure 6−15 shows that diastereomeric esters are formed when (*R*)-and (*S*)-2-butanol react with (+)-tartaric acid. We can represent the reaction schematically as follows:

(*R*)-and (*S*)-2-butanol				
plus	$\xrightarrow{\mathrm{H^+}}$	(*R*)-2-butyl (*R*, *R*)-tartrate	+	(*S*)-2-butyl (*R*, *R*)-tartrate
(*R*, *R*)-tartaric acid		diastereomers, *not* mirror images		

The diastereomers of 2-butyl tartrate have different physical properties, and they can be separated by conventional distillation, recrystallization, or chromatography. Separation of the diastereomers leaves us with two flasks, each containing one of the diastereomeric esters. The resolving agent is then cleaved from the separated enantiomers of 2-butanol by the reverse of the reaction used to make the ester. Adding an acid catalyst and an excess of water to an ester drives the equilibrium toward the acid and the alcohol:

$$\underset{\text{ester}}{\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}R'}} + \underset{\text{water}}{\mathrm{H{-}O{-}H}} \xrightleftharpoons{(\mathrm{H^+\ catalyst})} \underset{\text{acid}}{\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH}} + \underset{\text{alcohol}}{\mathrm{R'{-}OH}}$$

Hydrolysis of (*R*)-2-butyl tartrate gives (*R*)-2-butanol and (+)-tartaric acid, and hydrolysis of (*S*)-2-butyl tartrate gives (*S*)-2-butanol and (+)-tartaric acid. The recovered tartaric acid would probably be thrown away, since it is cheap and nontoxic. Many other chiral resolving agents are expensive, so they must be carefully recovered and recycled.

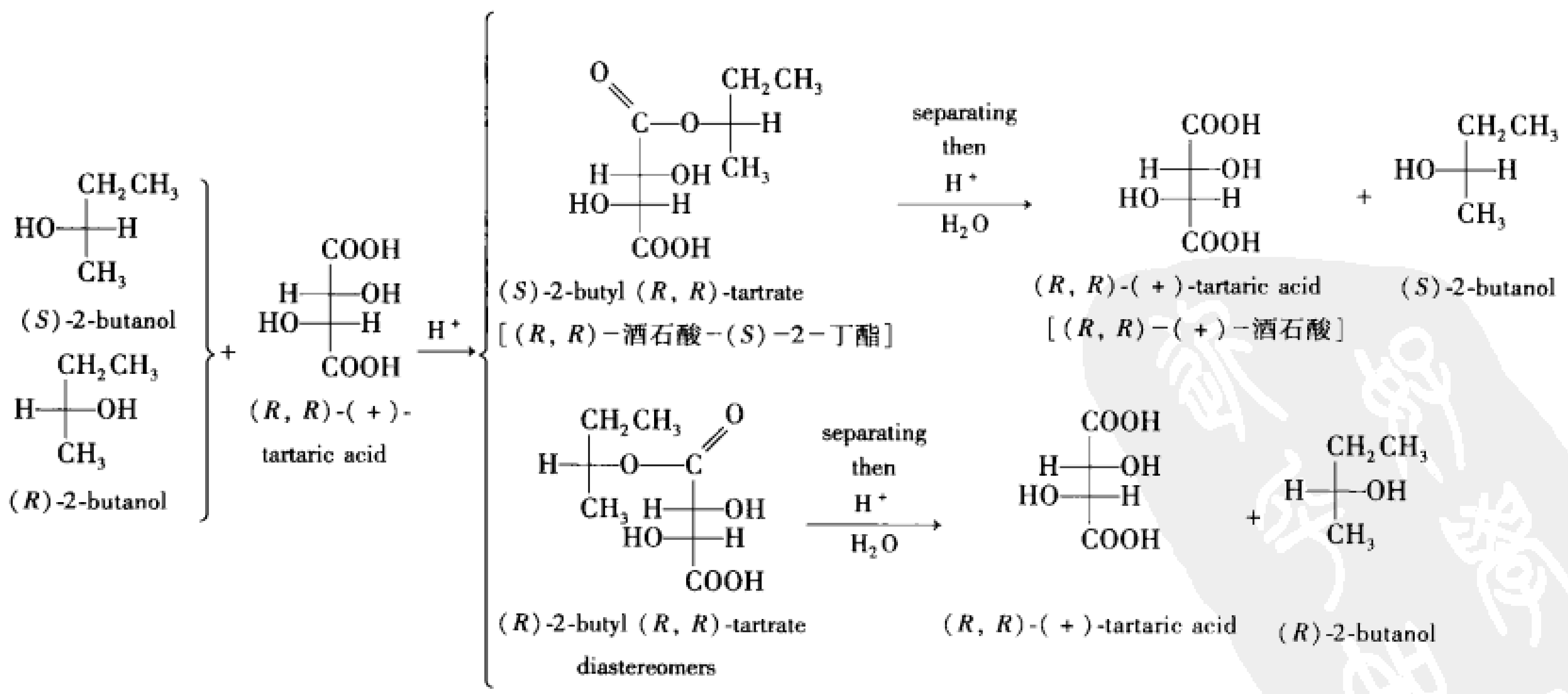


Figure 6−15 Formation of (*R*)-and (*S*)-2-butyl tartrate. The reaction of a pure enantiomer of one compound with a racemic mixture of another compound produces a mixture of diastereomers. Separation of the diastereomers, followed by hydrolysis, gives the resolved enantiomers.

PROBLEM 6-20

To show that (*R*)-2-butyl-(*R*, *R*)-tartrate and (*S*)-2-butyl-(*R*, *R*)-tartrate are not enantiomers, draw and name the mirror images of these compounds.

6-15B Chromatographic Resolution of Enantiomers

Chromatography is a powerful method for separating compounds. One type of chromatography involves passing a solution through a column containing particles whose surface tends to adsorb organic compounds. Compounds that are adsorbed strongly spend more time on the stationary particles; they come off the column later than less strongly adsorbed compounds, which spend more time in the mobile solvent phase.

In some cases, enantiomers may be resolved by passing the racemic mixture through a column containing particles whose surface is coated with chiral molecules. As the solution passes through the co-lumn, the enantiomers from weak complexes, usually through hydrogen bonding, with the chiral column packing. The solvent flows continually through the column, and the dissolved enantiomers gradually move along, retarded by the time they spend complexed with the column packing.

The special feature of this chromatography is the fact that the enantiomers form diastereomeric complexes with the chiral column packing. These diastereomeric complexes have different physical properties. They also have different binding energies and different equilibrium constants for complexation. One of the two enantiomers will spend more time complexed with the chiral column packing. The more strongly complexed enantiomer passes through the column more slowly and emerges from the column after the faster-moving (more weakly complexed) enantiomer.

Summary in Chinese

本章概要

一、手性、对映异构体与非对映异构体(chirality, enantiomers and diastereomers)

1. 手性(chirality or handedness):实物与其镜像不能重合,这一特征称为手性,具有这种特征的物质称为手性物质。

2. 立体中心与手性碳原子(stereocenter and chiral carbon atom):如果交换一个原子上的两个基团能够给出另一种立体异构体,则称这个原子为立体中心,它包括手性碳原子和顺/反异构烯烃中的双键碳原子。与四个不相同原子或基团相连接的碳原子称为手性碳原子,又称不对称碳原子(asymmetric carbon atom)。有 n 个手性碳原子的分子最多可有 2^n 个立体异构体。

3. 手性分子(chiral molecules):凡是与自身镜像不能重合的分子都是手性分子,能重合的为非手性分子。大多数手性有机化合物分子中含有手性碳原子。有些有机化合物具有手性,但没有手性中心。这些手性化合物具有手性轴或手性面,如丙二烯型化合物、螺环型化合物和联苯型化合物。邻位带有大基团的联苯型化合物分子,连接两个苯环的碳碳单键,由于空阻原因室温下不能旋转而形成的对映体又称为构象对映体。

4. 对映异构体(enantiomers):两个互为实物与镜像关系的手性分子,被称为一对对映异构体,简称对映体。两个对映异构体的等量混合物,称为外消旋体(racemate or racemic mixture)。外消旋体一般通过与另一种纯手性试剂反应生成非对映异构体来进行拆分(resolution),或通过手性制备柱进行拆分。除了旋光方向不同之外,一对对映异构体具有相同的物理性质,如沸点、熔点、溶解性等。在无手性反应物或手性

催化剂存在条件下,对映异构体具有相同的化学反应性质。

5. 非对映异构体(diastereomers):相互不具有实物与镜像关系的立体异构体,被称为非对映异构体,简称非对映体。非对映异构体具有不同的物理性质和化学性质。

二、利用对称面判断分子是否具有手性

1. 对称面(plane of symmetry or internal mirror plane of symmetry):如果一个平面能够把分子平分为镜像对映的两半,该平面称为分子的对称面。

2. 内消旋体(mesomers):同时具有手性碳原子和分子内对称面的分子称为内消旋体,是一种非手性分子。

3. 判断分子手性:凡是具有对称面的分子一定是非手性分子,但不具有对称面的分子不一定都是手性分子。最可靠的方法是通过比对分子与其镜像是否能重合的方法来判断分子是否具有手性。对于室温下可发生单键旋转或环骨架扭转的分子,在判断分子是否具有手性时应考虑分子最对称的构象。如果分子的一种手性构象能够在室温下与其对映的构象相互转变,则可判断分子是非手性的。

三、手性分子构型表示方法

1. 手性分子的构型可用球棍模型(ball-and-stick model)、透视结构式或三维结构式(perspective structure or three-dimensional formula)或费歇尔投影式(Fischer projection)来表示,其中费歇尔投影式对于表示两个或两个以上不对称碳原子的手性分子构型十分有用。

2. 费歇尔投影式:费歇尔投影式中表示共价键的十字线交叉点代表手性碳原子,横线表示伸向纸面前方的键,而竖线表示伸向纸面后方的键。费歇尔投影式在纸面上转 $n \times 180°$(n 为正整数),不会改变原子或基团的立体化学关系,旋转后的投影式与原投影式表示同一种分子构型。但如果将费歇尔投影式在纸面上转 $n \times 90°$或将其翻转 180°时,投影式所表示的分子构型为原投影式的对映体。

四、手性分子的 *R/S* 与 D/L 命名

1. *R/S* 标记法:首先按照 Cahn-Ingold-Prelog 规则,确定与手性碳原子相连的四个不同原子或基团的优先性,然后将优先性最低的原子或基团指向外,观察其他三个原子或基团的空间相对位置,如按优先性由高到低为顺时针排列,手性碳标记为 *R* 构型;反之,标记为 *S* 构型。交换一个手性碳上的任意两个原子或基团可使 *R* 构型变为 *S* 构型,反之亦然。*R/S* 标记可用于命名所有含手性中心的有机化合物和含有三个或三个以上不对称碳原子的内消旋体。

2. D/L 标记法:D/L 标记主要用于糖、氨基酸及蛋白质化学中。D/L 命名以甘油醛(glyceraldehyde)为参照物,将标准费歇尔投影式中手性碳上的羟基在右边的甘油醛标记为 D 构型,在左边的标记为 L 构型。在保持甘油醛手性碳构型不变的情况下,凡是能由 D 型甘油醛衍生出来的化合物均为 D 构型,而由 L 型甘油醛衍生出来的化合物均为 L 构型。

五、手性分子的旋光性(rotation of polarized light by chiral molecules)

1. 旋光性:手性分子的一个重要物理性质是可以使偏光平面向右或向左偏转。因此,手性化合物又被称为光活性化合物(optically active compounds)。一对对映异构体旋转偏光平面的能力大小相等,但方向相反。因此,外消旋体为光学非活性的。

2. 比旋光(specific rotation):手性分子使偏光平面偏转的方向和大小可以通过旋光仪(polarimeter)进行测量。通常采用比旋光[α]来衡量化合物的旋光性,即纯手性化合物质量浓度为 1 g/mL 时,在 1 dm 长的测量池中测得的旋光度。比旋光[α]可用下式计算:

$$[\alpha]_{D}^{t} = \frac{\alpha}{\rho \cdot l}$$

式中:α 为测得的旋光度;ρ 为纯手性化合物溶液的质量浓度;l 为试管长度;D 为钠灯光源;t 为测试温度。

旋光方向向右用"+"号表示,向左用"-"号表示。如果已知一种纯手性化合物的比旋光,则可通过测量对映体混合物的比旋光计算出此化合物的光学纯度(optical purity)。目前,光学纯度一般采用对映体

过量(enantiomeric excess,简写为 ee)来表示。

六、立体异构体分类总结

- 立体异构体 (stereoisomers or configurational isomers)
  - 非对映异构体 (diastereomers)
    - 顺/反异构体 (cis-trans isomers or geometric isomers)
    - 其他非对映异构体 (other diastereomers)
  - 对映异构体 (enantiomers)

Essential Problem-Solving Skills in Chapter 6

1. Classify molecules as chiral or achiral, and identify mirror planes of symmetry.
2. Identify asymmetric carbon atoms, and name them using the (*R*) and (*S*) nomenclature.
3. Calculate specific rotations from polarimetry data.
4. Draw all stereoisomers of a given structure.
5. Identify enantiomers, diastereomers, and meso compounds.
6. Draw correct Fischer projections of asymmetric carbon atoms.
7. Explain how the physical properties differ for different types of stereoisomers.
8. Suggest how to separate different types of stereoisomers.

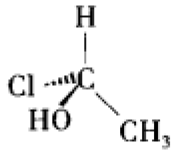
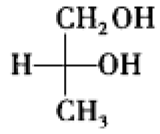
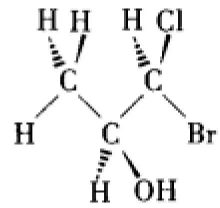
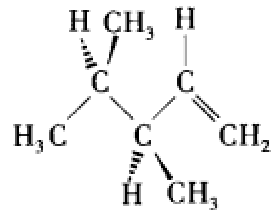
Study Problems

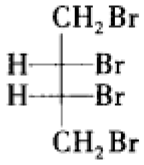
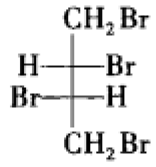
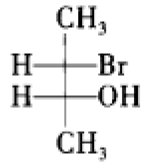
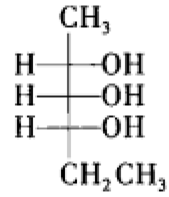
6–21 Briefly define each term and give an example.

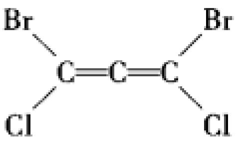
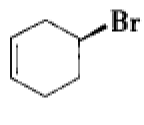
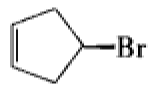
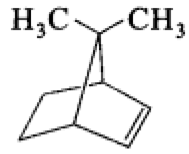
(a) (*R*) and (*S*)
(b) chiral and achiral (手性和非手性)
(c) chiral carbon atom (手性碳原子)
(d) cis and trans (顺反式)
(e) asymmetric carbon atom
(f) isomers (异构体)
(g) constitutional isomers (构造异构体)
(h) stereoisomers (立体异构体)
(i) enantiomers (对映体)
(j) Fischer projection (费歇尔投影式)
(k) diastereomers (非对映异构体)
(l) chirality center (手性中心)
(m) optical isomers (光学异构体)
(n) meso (内消旋)
(o) stereocenter (立体中心)
(p) racemic mixture (外消旋混合物)
(q) specific rotation (比旋光)
(r) dextrorotatory (右旋)
(s) (±) and (*d*, *l*)
(t) absolute configuration (绝对构型)
(u) relative configuration (相对构型)
(v) D and L configurations

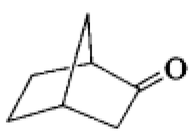
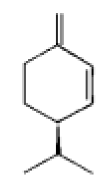
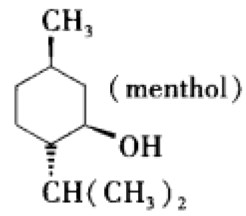
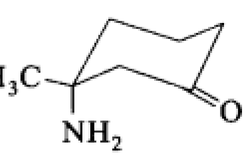
6–22 For each structure,

1. Star (*) any asymmetric carbon atoms.
2. Label each asymmetric carbon as (*R*) or (*S*).
3. Draw in any internal mirror planes of symmetry.
4. Label the structure as chiral or achiral.
5. Label any meso structures.

(a)  (b)  (c)  (d) 

(e)  (f)  (g)  (h) 

(i)  (j)  (k)  (l) 

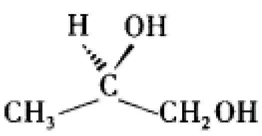
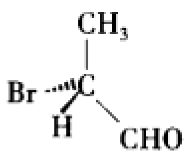
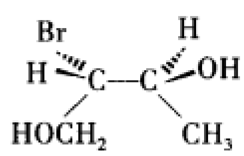
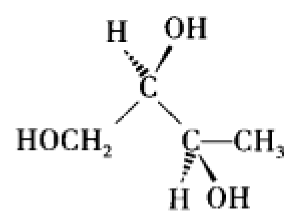
(m)  (n)  (o)  (menthol) (p) 

6–23 For each of the compounds described by the following names,

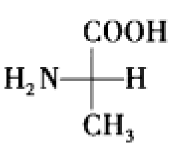
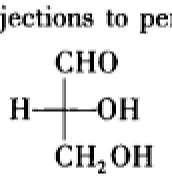
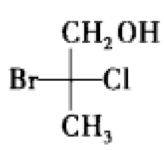
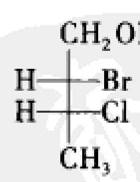
1. Draw a three-dimensional representation.
2. Star (*) each chirality center.
3. Draw any planes of symmetry.
4. Draw any enantiomer.
5. Draw any diastereomers.
6. Label each structure you have drawn as chiral or achiral.

(a) (S)-2-chlorobutane
(b) (R)-1,1,2-trimethylcyclohexane
(c) (2R, 3S)-2,3-dibromohexane
(d) (1R,2R)-1, 2-dibromocyclohexane
(e) *meso*-3,4-hexanediol, $CH_3CH_2CH(OH)CH(OH)CH_2CH_3$
(f) (±)-3,4-hexanediol

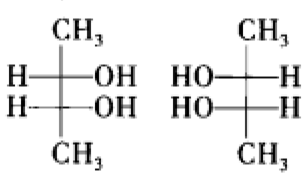
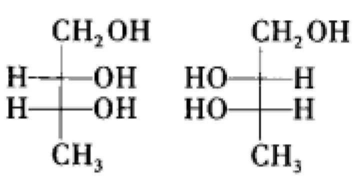
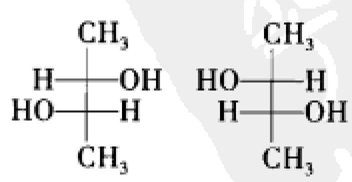
6–24 Convert the following perspective formulas to Fischer projections.

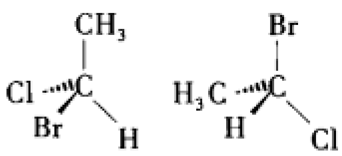
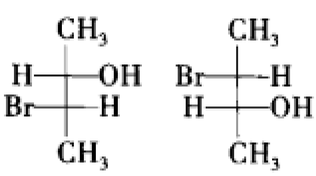
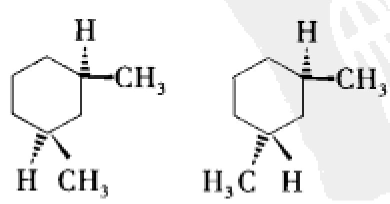
(a)  (b)  (c)  (d) 

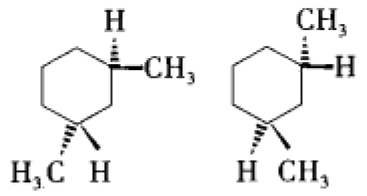
6–25 Convert the following Fischer projections to perspective formulas.

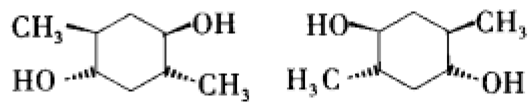
(a)  (b)  (c)  (d) 

6–26 Give the stereochemical relationships between each pair of structures. Examples are same compound, structural isomers, enantiomers, diastereomers.

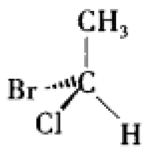
(a)  (b)  (c) 

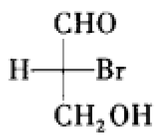
(d)  (e)  (f) 

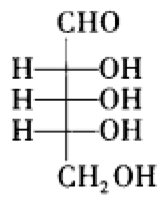
(g) 

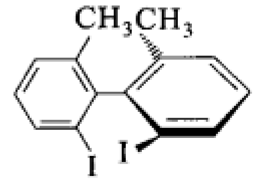
(h) 

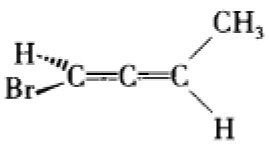
6–27 Draw the enantiomer, if any, for each structure.

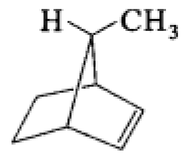
(a) 

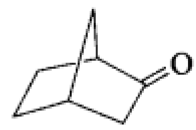
(b) 

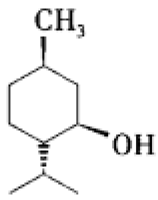
(c) 

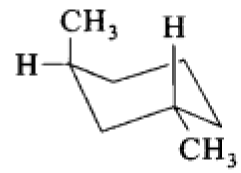
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

6–28 (+)-Tartaric acid has a specific rotation of +12.0°. Calculate the specific rotation of a mixture of 68% (+)-tartaric acid and 32% (–)-tartaric acid.

6–29 The specific rotation of (*S*)-2-iodobutane is +15.90°.

(a) Draw the structure of (*S*)-2-iodobutane.

(b) Predict the specific rotation of (*R*)-2-iodobutane.

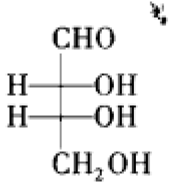
(c) Determine the percentage composition of a mixture of (*R*)-and (*S*)-2-iodobutane with a specific rotation of –7.95°.

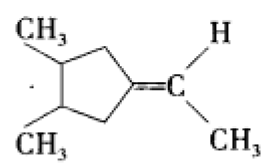
***6–30** For each structure,

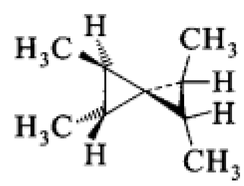
1. Draw all the stereoisomers.

2. Label each structure as chiral or achiral.

3. Give the relationships between the stereoisomers (enantiomers, diastereomers).

(a) 

(b) 

(c) 

***6–31** Draw all the stereoisomers of 1,2,3-trimethylcyclopentane, and give the relationships between them.

***6–32** If you think you know your definitions, try this difficult problem.

(a) Draw all the stereoisomers of 2,3,4-tribromopentane. (Using Fischer projections may be helpful.) You should find two meso structures and one pair of enantiomers.

(b) Star (*) the asymmetric carbon atoms, and label each as (*R*) or (*S*).

(c) In the meso structures, show how C3 is not asymmetric, nor is it a chirality center, yet it is stereogenic.

(d) In the enantiomers, show how C3 is not stereogenic in this diastereomer.

Chapter 7

Alkyl Halides: Nucleophilic Substitution and Elimination

7-1 Introduction

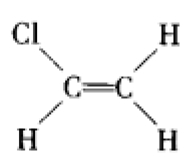
Our study of organic chemistry is organized into families of compounds classified by their functional groups. In this chapter, we consider the properties and reactions of alkyl halides. We use their reactions to introduce substitution and elimination, two of the most important types of reactions in organic chemistry. Stereochemistry (Chapter 6) will play a major role in our study of these reactions. Many other reactions show similarities to substitution and elimination, and the techniques introduced in this chapter will be used throughout our study of organic reactions.

Ther are three major classes of organohalogen compounds: the alkyl halides, the vinyl halides, and the aryl halides. An **alkyl halide** simply has a halogen atom bonded to one of the sp^3 hybrid carbon atoms of an alkyl group. A **vinyl halide** has a halogen atom bonded to one of the sp^2 hybrid carbon atoms of an alkene. An **aryl halide** has a halogen atom bonded to one of the sp^2 hybrid carbon atoms of an aromatic ring. The chemistry of vinyl halides and aryl halides is different from that of alkyl halides because their bonding and hybridization are different. We consider the reactions of vinyl halides and aryl halides in later chapters. The structures and uses of some representative alkyl halides, vinyl halides, and aryl halides are shown here.

Alkyl halides

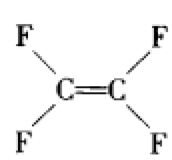
$CHCl_3$	$CHClF_2$	$CCl_3—CH_3$	$CF_3—CHClBr$
chloroform	Freon-22®	1,1,1-trichloroethane	Halothane
(氯仿)	(氟利昂)	(1,1,1-三氯乙烷)	(三氟溴氯乙烷)
solvent	refrigerant	cleaning fluid	nonflammable anesthetic

Vinyl halides



vinyl chloride(乙烯基氯)

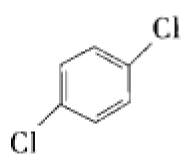
monomer for poly (vinyl chloride)



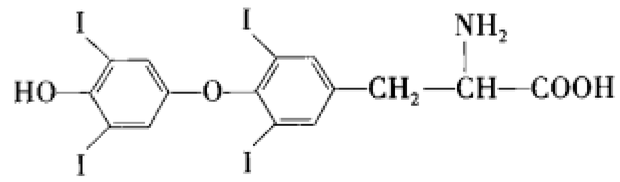
tetrafluoroethylene(TFE, 四氟乙烯)

monomer for Teflon®

Aryl halides



para-dichlorobenzene(对二氯苯)
mothballs



thyoxine(甲状腺素)
thyroid hormone(甲状腺激素)

7−2 Common Uses of Alkyl Halides

7−2A Solvents

Alkyl halides are used primarily as industrial and household solvents. Carbon tetrachloride (CCl_4) was once used for dry cleaning, spot removing, and other domestic cleaning, Carbon tetrachloride is toxic and carcinogenic (causes cancer), however, so dry cleaners now use 1,1,1-trichloroethane and other solvents instead.

Methylene chloride (CH_2Cl_2) and chloroform ($CHCl_3$) are also good solvents for cleaning and degreasing work. Methylene chloride was once used to dissolve the caffeine from coffee beans to produce decaffeinated coffee. Concerns about the safety of coffee with residual traces of methylene chloride prompted coffee producers to use liquid carbon dioxide instead. Chloroform is more toxic and carcinogenic than methylene chloride; it has been replaced by methylene chloride and other solvents in most industrial degreasers and paint removers.

Even the safest halogenated solvents, such as methylene chloride and 1,1,1-trichloroethane, should be used carefully, however. They are all potentially toxic and carcinogenic, and they dissolve the fatty oils that protect skin, causing a form of dermatitis.

7−2B Reagents

Many syntheses use alkyl halides as starting materials for making more complex molecules. The conversion of alkyl halides to organometallic reagents (compounds containing carbon-metal bonds) is a particularly important tool for organic synthesis.

7−2C Anesthetics

Chloroform ($CHCl_3$) was the first substance found to produce general anesthesia, opening new possibilities for careful surgery with a patient who is unconscious and relaxed. Chloroform, is toxic and carcinogenic, however, and it was soon abandoned in favor of safer anesthetics. A less toxic anesthetic is a mixed alkyl halide, $CF_3CHClBr$, which goes by the trade name Halothane. Ethyl chloride is often used as a topical anesthetic for minor procedures, When sprayed on the skin, its evaporation (bp 12 ℃) cools the area and enhances the numbing effect.

7−2D Freons: Refrigerants and Foaming Agents

The **freons** (also called *chlorofluorocarbons*, or CFCs) are fluorinated haloalkanes that were developed to replace ammonia as a refrigerant gas. Ammonia is toxic, and leaking refrigerators often killed people who were working or sleeping nearby, Freon-12®, CF_2Cl_2, was at one time the most widely used refri-gerant. Low-boiling freons

(such as Freon-11®, CCl_3F) were once used as *foaming agents* that were added to a plastic to vaporize and form a froth that hardens into a plastic foam. The release of freons into the atmosphere has raised concerns about their reactions with the earth's protective ozone layer. It appears that CFCs gradually diffuse up into the stratosphere, where the chlorine atoms catalyze the decomposition of ozone (O_3) into oxygen (O_2). Most scientists blame the freon-catalyzed depletion of ozone for the "hole" in the ozone layer that has been detected over the South Pole.

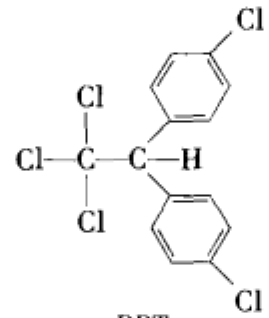
International treaties have limited the future production and use of the ozonedestroying freons. Freon-12 has been replaced in aerosol cans by low-boiling hydrocarbons or carbon dioxide. In refrigerators and automotive air conditioners, Freon-12 has been replaced by Freon-22®, $CHClF_2$. Freons with C—H bonds (such as Freon-22), called HCFCs, are generally destroyed at lower altitudes before they reach the stratosphere. Propane, CO_2, and HCFC-123 ($CHCl_2CF_3$) are used as a substitutes for Freon-11 in making plastic foams.

7-2E Pesticides

Alkyl halides have contributed to human health through their use as insecticides. Since antiquity, people have died from famine and disease caused or carried by mosquitoes, fleas, lice, and other vermin. The "black death" of the Middle Ages wiped out nearly a third of the population of Europe through infection by the flea-borne bubonic plague. Whole regions of Africa and tropical America were uninhabited and unexplored because people could not survive insect-borne diseases such as malaria, yellow fever, and sleeping sickness.

Arsenic compounds, nicotine, and other crude insecticides were developed in the nineteenth century, but these compounds are just as toxic to birds, animals, and people as they are to insects, Their use is extremely hazardous, but a hazardous insecticide was still preferable to certain death by disease or starvation.

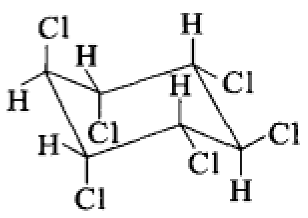
The war against insects changed dramatically in 1939 with the discovery of DDT (Figure 7-1). DDT is extremely toxic to insects, but its toxicity in mammals is quite low. About an ounce of DDT is required to kill a person, but that same amount of insecticide protects an acre of land against locusts or mosquitoes. As with many inventions, DDT showed undesired side effects. It is a long-lasting insecticide, and its residues accumulate in the environment. The widespread use of DDT as an agricultural insecticide led to the development of substantial DDT concentrations in wildlife, causing declines in several species. In 1972, DDT was banned by the U. S. Environmental Protection Agency for use as an agricultural insecticide. It is still used as a last resort, however, in countries where insect-borne diseases threaten human life.



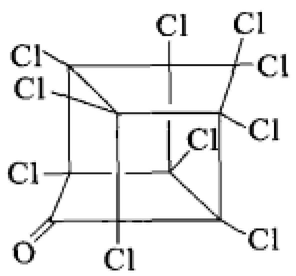
DDT

Figure 7-1 Structure of DDT. DDT is Dichloro Diphenyl Trichloroethane, or 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl) ethane. DDT was the first chlorinated insecticide. Its use rendered large parts of the world safe from insect-borne disease and starvation, but it accumulated in the environment.

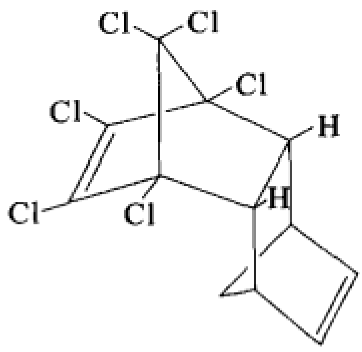
Many other chlorinated insecticides have been developed. Some of them also accumulate in the environment, gradually producing toxic effects in wildlife. Others can be used with little adverse impact if they are applied properly. Because of their persistent toxic effects, chlorinated insecticides are rarely used in agriculture. They are generally used when a potent insecticide is needed to protect life or property. For example, lindane is used in shampoos to kill lice, and chlordane is used to protect wooden buildings from termites. The structures of some chlorinated insecticides are shown next.



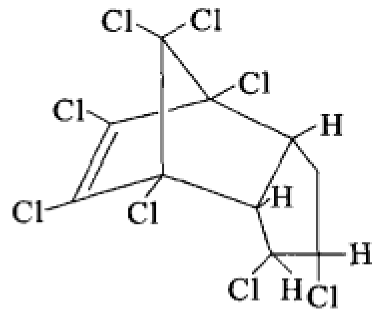
lindane
（林丹，高丙体六六六）



kepone
（十氯酮）



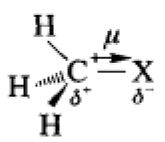
aldrin
（艾氏剂，氯甲桥萘）



chlordane
（氯丹，八氯代甲桥茚）

7-3 Structure of Alkyl Halides

In an alkyl halide , the halogen atom is bonded to an sp^3 hybrid carbon atom. The carbon-halogen bond in an alkyl halide is polar because halogen atoms are more electronegative than carbon atoms. Most reactions of alkyl halides result from breaking this polarized bond. The carbon atom has a partial positive charge, making it somewhat electrophilic. A nucleophile can attack this electrophilic carbon, or the halogen atom can leave as a halide ion, taking the bonding pair of electrons with it. By serving as a leaving group, the halogen can be eliminated from the alkyl halide, or it can be replaced (substituted for) by a wide variety of functional groups. This versatility allows alkyl halides to serve as intermediates in the synthesis of many other functional groups.



$\mu = 4.8 \times \delta \times d$
where δ is the charge and d is the bond length.

The electronegativities of the halogens *increase* in the order

	I	<	Br	<	Cl	<	F
electronegativity:	2.7		3.0		3.2		4.0

The carbon-halogen bond lengths *increase* as the halogen atoms become bigger (larger atomic radii) in the order

	C—F	<	C—Cl	<	C—Br	<	C—I
bond length:	1.38Å		1.78Å		1.94Å		2.14Å

These two effects oppose each other, with the larger halogens having longer bonds but weaker electronegativities. The overall result is that the bond dipole moments increase in the order

	C—I	<	C—Br	<	C—F	<	C—Cl
dipole moment, μ:	1.29D		1.48D		1.51D		1.56D

A *molecular* dipole moment is the vector sum of the individual bond dipole moments. Molecular dipole moments are not easy to predict because the depend on the bond angles and other factors that vary with the specific molecule. Table 7-1 lists the experimentally measured dipole moments of the halogenated methanes. Notice how the four symmetrically oriented polar bonds of the carbon tetrahalides cancel to give a molecular dipole moment of zero.

TABLE 7-1 Molecular Dipole Moments of Methyl Halides

X	CH_3X	CH_2X_2	CHX_3	CX_4
F	1.82 D	1.97 D	1.65 D	0
Cl	1.94 D	1.60 D	1.03 D	0

Continue

X	CH_3X	CH_2X_2	CHX_3	CX_4
Br	1.79 D	1.45 D	1.02 D	0
I	1.64 D	1.11 D	1.00 D	0

7-4 Physical Properties of Alkyl Halides

7-4A Boiling Points

Two types of intermolecular forces influence the boiling points of alkyl halides. The London force is the strongest intermolecular attraction in alkyl halides. London forces are *surface* attractions, resulting from coordinated temporary dipoles. Molecules with larger surface areas have larger London attractions, resulting in higher boiling points. Dipole-dipole attractions (arising from the polar C—X bond) also affect the boiling points, but to a smaller extent.

Molecules with higher molecular weights generally have higher boiling points because they are heavier (and therefore slower moving), and they have greater surface area. The surface areas of the alkyl halides vary with the surface areas of halogens. We can get an idea of the relative surface areas of halogen atoms by considering their van der Waals radii. According to the radius of the fluorine, an alkyl fluoride has nearly the same surface area as the corresponding alkane; thus its London attractive forces are similar. The alkyl fluoride has a larger dipole monment, however, so the total attractive forces are slightly greater in the alkyl fluoride, giving it a higher boiling point. For example, the boiling point of *n*-butane is 0 ℃, while that of *n*-butyl fluoride is 33 ℃.

van der Waals Halogen	Radius/(10^{-8}cm)
F	1.35
Cl	1.8
Br	1.95
I	2.15
H(for comparison)	1.2

The other halogens are considerably larger than fluorine, giving them more surface area and raising the boiling points of their alkyl halides. With a boiling point of 78 ℃, *n*-butyl chloride shows the influence of chlorine's much larger surface area. This trend continues with *n*-butyl bromide (bp 102 ℃) and *n*-butyl iodide (bp 131 ℃). Table 7-2 lists the boiling points and densities of some simple alkyl halides. Notice that compounds with branched, more spherical shapes have lower boiling points as a result of their smaller surface areas. For example, *n*-butyl bromide has a boiling point of 102 ℃, while the more spherical *t*-butyl bromide has a boiling point of only 73 ℃. This effect is similar to the one we saw with alkanes.

TABLE 7-2 Properties of Some Simple Alkyl Halides

Compound	Molecular Weight	Boiling Point/℃	Density/($g \cdot mL^{-1}$)
CH_3—F	34	-78	
CH_3—Cl	50.5	-24	0.92
CH_3—Br	95	4	1.68
CH_3—I	142	42	2.28
CH_2Cl_2	85	40	1.34
$CHCl_3$	119	61	1.50
CCl_4	154	77	1.60
CH_3CH_2—F	48	-38	0.72

Continue

Compound	Molecular Weight	Boiling Point/ ℃	Density/($g \cdot mL^{-1}$)
$CH_3CH_2—Cl$	64.5	12	0.90
$CH_3CH_2—Br$	109	38	1.46
$CH_3CH_2—I$	156	72	1.94
$CH_3CH_2CH_2—F$	62	3	0.80
$CH_3CH_2CH_2—Cl$	78.5	47	0.89
$CH_3CH_2CH_2—Br$	123	71	1.35
$CH_3CH_2CH_2—I$	170	102	1.75
$(CH_3)_2CH—Cl$	78.5	36	0.86
$(CH_3)_2CH—Br$	123	59	1.31
$(CH_3)_2CH—I$	170	89	1.70
$CH_3CH_2CH_2CH_2—F$	76	33	0.78
$CH_3CH_2CH_2CH_2—Cl$	92.5	78	0.89
$CH_3CH_2CH_2CH_2—Br$	137	102	1.28
$CH_3CH_2CH_2CH_2—I$	184	131	1.62
$(CH_3)_3C—Cl$	92.5	52	0.84
$(CH_3)_3C—Br$	137	73	1.23
$(CH_3)_3C—I$	184	100	1.54

PROBLEM 7-1

For each pair of compounds, predict which compound has the higher boiling point. Check Table 7-2 to see if your prediction was right, then explain why that compound has the higher boiling point.

(**a**) isopropyl bromide and *n*-butyl bromide

(**b**) isopropyl chloride and *t*-butyl bromide

(**c**) *n*-butyl bromide and *n*-butyl chloride

7-4B Densities

Table 7-2 also shows the densities of common alkyl halides. Like their boiling points, their densities follow a predictable trend. Alkyl fluorides and alkyl chlorides (those with just one chlorine atom) are less dense than water (1.00 g/mL). Alkyl chlorides with two or more chlorine atoms are denser than water, and all alkyl bromides and alkyl iodides are denser than water.

PROBLEM 7-2

When water is shaken with hexane, the two liquids separate into two phases. Show which compound is present in the top and which in the bottom phase. When water is shaken with chloroform, a similar two-phase system results. Again, show which compound is present in each phase. Explain the difference in the two experiments.

7-5 Preparation of Alkyl Halides

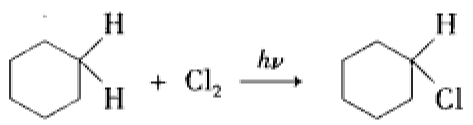
Most syntheses of alkyl halides exploit the chemistry of functional groups we have not yet covered. For now, we only review free-radical halogenation. The other syntheses are discussed in subsequent chapters.

7−5A Free-Radical Halogenation

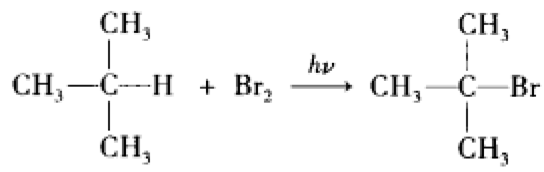
Although we discussed its mechanism at length in Section 5−3, free-radical halogenation is rarely an effective method for the synthesis of alkyl halides. It usually produces mixtures of products because there are different kinds of hydrogen atoms that can be abstracted. Also, more than one halogen atom may react, giving multiple substitutions. For example, the chlorination of propane can give a messy mixture of products.

$$CH_3{-}CH_2{-}CH_3 + Cl_2 \xrightarrow{h\nu} \begin{cases} CH_3{-}CH_2{-}CH_2Cl + CH_3{-}CHCl{-}CH_3 \\ + CH_3{-}CHCl{-}CH_2Cl + CH_3{-}CCl_2{-}CH_3 \\ + CH_3{-}CH_2{-}CHCl_2 + \text{others} \end{cases}$$

In industry, free-radical halogenation is sometimes useful because the reagents are cheap, the mixture of products can be separated by distillation, and each of the individual products is sold separately. In a laboratory. however, we need a good yield of one particular product. Free-radical halogenation rarely provides good selectivity and yield, so it is seldom used in the laboratory. Laboratory syntheses using free-radical halogenation are generally limited to specialized compounds that give a single major product, such as the following examples.



cyclohexane chlorocyclohexane (50%)

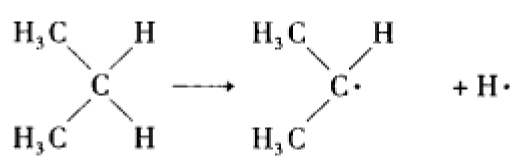


isobutane *t*-butyl bromide (90%)

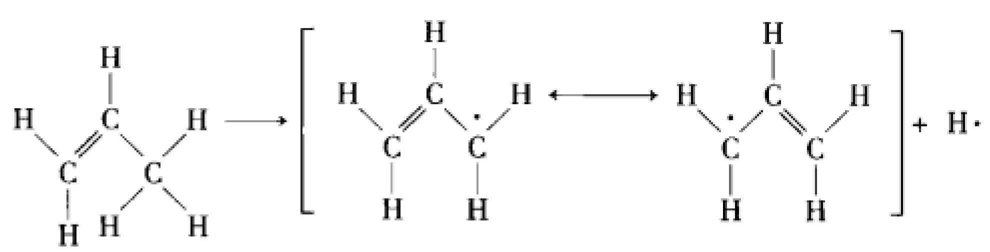
All the hydrogen atoms in cyclohexane are equivalent, and free-radical chlorination gives a usable yield of chlorocyclohexane. Formation of dichlorides and trichlorides is possible, but these side reactions are controlled by using only a small amount of chlorine and an excess of cyclohexane. Free-radical bromination is highly selective (Section 5−14), and it gives good yields of products that have one type of hydrogen atom that is more reactive than the others. Isobutane has only one tertiary hydrogen atom, and this atom is preferentially abstracted to give a tertiary free radical, In general, however, we are not inclined to use free-radical halogenation in the laboratory because it tends to be plagued by mixtures of products.

7−5B Allylic Bromination

Although free-radical halogenation is not a good synthetic method in most cases, free-radical bromination of alkenes can be carried out in a highly selective manner. An **allylic** position is a carbon atom next to a carbon-carbon double bond. Allylic intermediates (cations, radicals, and anions) are stabilized by resonance with the double bond, allowing the charge or radical to be delocalized, The following bond dissociation enthalpies show that less energy is required to form a resonance-stabilized primary allylic radical than a typical secondary radical.

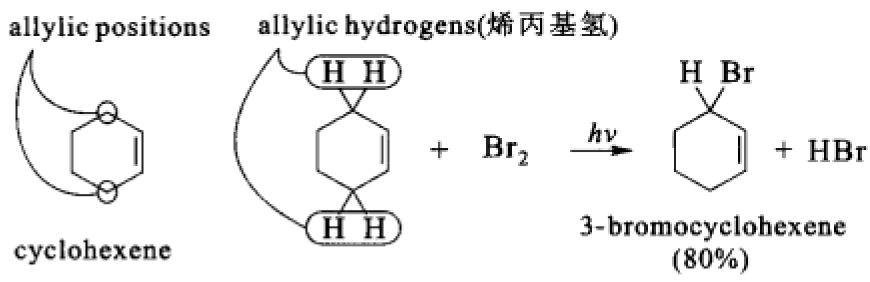


$\Delta H = +397$ kJ/mol

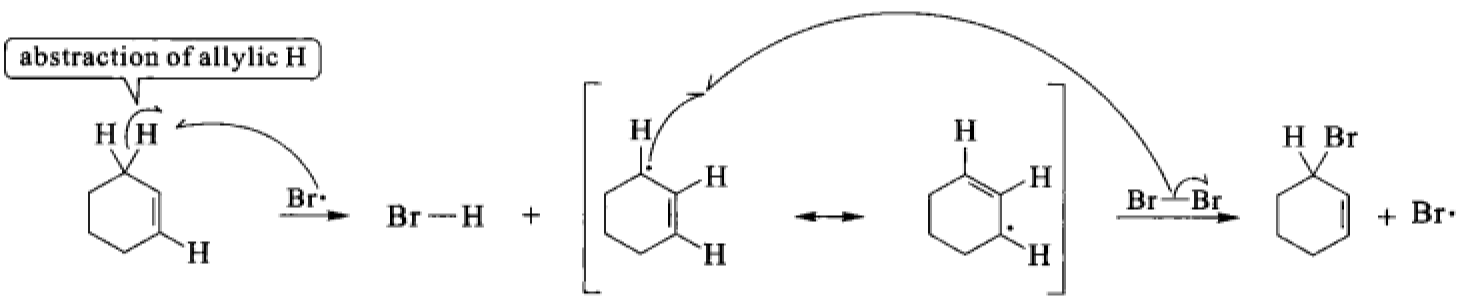


$\Delta H = +364$ kJ/mol

We have seen (Section 5-13) that bromination is highly selective, with only the most stable radical being formed. If there is an allylic position, the allylic radical is usually the most stable of the radicals that might be formed. For example, consider the free-radical bromination of cyclohexene. Under the right conditions, free-radical bromination of cyclohexene can give a good yield of 3-bromocyclohexene, where bromine has substituted for an allylic hydrogen on the carbon atom next to the double bond.



The mechanism is similar to other free-radical halogenations. A bromine radical abstracts an allylic hydrogen atom to give a resonance-stabilized allylic radical. This radical reacts with Br_2, regenerating a bromine radical that continues the chain reaction.



cyclohexene allylic radical(烯丙基自由基) allylic bromide(烯丙基溴)

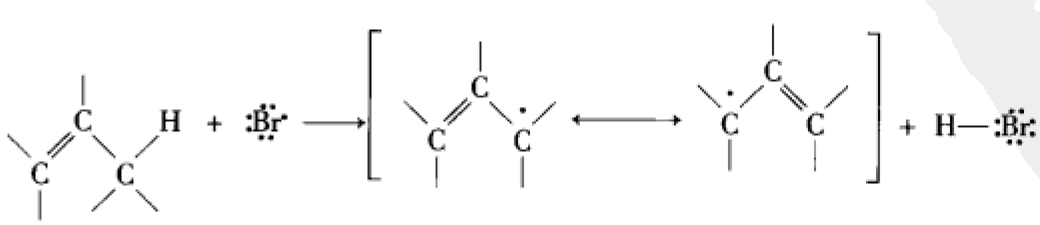
The general mechanism for allylic bromination shows that either end of the resonance-stabilized allylic radical can react with bromine to give products. In one of the products the bromine atom appears in the same position where the hydrogen atom was abstracted. The other product results from reaction at the carbon atom that bears the radical in the second resonance form of the allylic radical. This second compound is said to be the product of an *allylic shift*.

MECHANISM 7-1 Allylic Bromination

Initiation Step: Bromine absorbs light, causing formation of radicals.

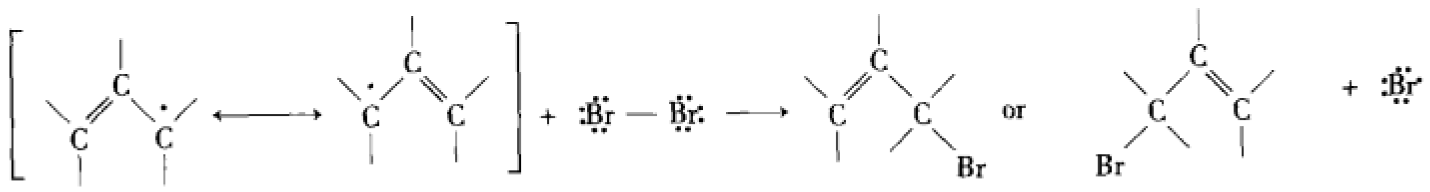
$$:\ddot{Br}-\ddot{Br}: \xrightarrow{h\nu} 2\,:\ddot{Br}\cdot$$

First Propagation Step: A bromine radical abstracts an allylic hydrogen.



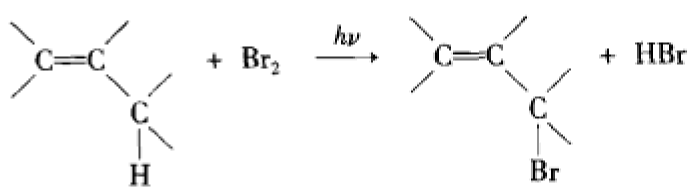
allylic radical

Second Propagation Step: Either radical carbon can react with bromine.



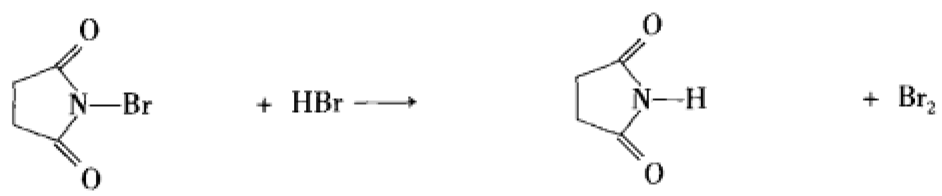
allylic shift(烯丙基位移)

Overall reaction



an allylic hydrogen   an allylic bromide

A large concentration of bromine must be avoided because bromine can add to the double bond (Chapter 9). *N*-Bromosuccinimide (NBS) is often used as the bromine source in free-radical brominations because it combines with the HBr side product to regenerate a constant low concentration of bromine. No additional bromine is needed because most samples of NBS contain traces of Br_2 to initiate the reaction.



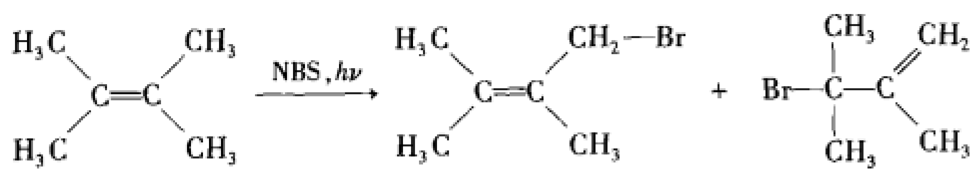
N-bromosuccinimide(NBS)
(*N*-溴代丁二酰亚胺)

regenerates a low concentration of Br_2

Allylic halogenation is discussed in more detail in Chapter 11.

PROBLEM 7-3

The light-catalyzed reaction of 2,3-dimethyl-2-butene with *N*-bromosuccinimide(NBS) gives two products:



2,3-dimethyl-2-butene

(a) Give a mechanism for this reaction, showing how the two products arise as a consequence of the resonance-stabilized intermediate.

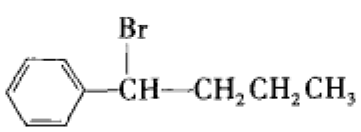
(b) The bromination of cyclohexene using NBS gives only one major product. Explain why there is no second product from an allylic shift.

PROBLEM 7-4

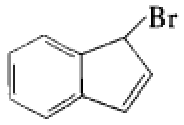
Show how free-radical halogenation might be used to synthesize the following compounds. In each case, explain why we expect to get a single major product.

(a) 1-chloro-2,2-dimethylpropane (neopentyl chloride)

(b) 2-bromo-2-methylbutane

(c) 

1-bromo-1-phenylbutane(1-溴-1-苯基丁烷)

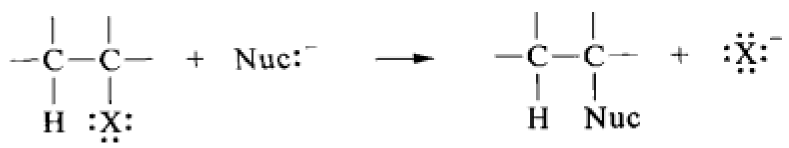
(d) 

7-6 Reactions of Alkyl Halides: Substitution and Elimination

Alkyl halides are easily converted to many other functional groups. The halogen atom can leave with its bonding pair of electrons to form a stable halide ion; we say that a halide is a good **leaving group.** When another atom replaces the halide ion, the reaction is a **substitution.** When the halide ion leaves with another atom or ion (often H^+), the reaction is an **elimination.** In many eliminations, a molecule of H—X is lost from the alkyl halide to give an alkene, These eliminations are called **dehydrohalogenations** because a hydrogen halide has been removed from the alkyl halide, Substitution and elimination reactions often compete with each other.

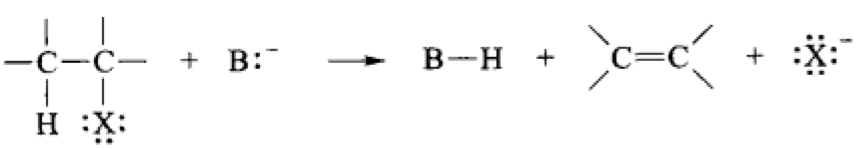
In a **nucleophilic substitution**, a nucleophile ($Nuc:^-$) replaces a leaving group ($:\ddot{X}:^-$) from a carbon atom, using its lone pair of electrons to form a new bond to the carbon atom.

Nucleophilic substitution



In an elimination, both the halide ion and another substituent are lost. A new π bond is formed.

Elimination



In the elimination (a dehydrohalogenation), the reagent ($B:^-$) reacts as a base, abstracting a proton from the alkyl halide, Most nucleophiles are also basic and can engage in either substitution or elimination, depending on the alkyl halide and the reaction conditions.

Besides alkyl halides, many other types of compounds undergo substitution and elimination reactions. Substitutions and eliminations are introduced in this chapter using the alkyl halides as examples. In later chapters, we encounter substitutions and eliminations of other types of compounds.

PROBLEM 7-5

Give the structures of the substitution products expected when 1-bromohexane reacts with

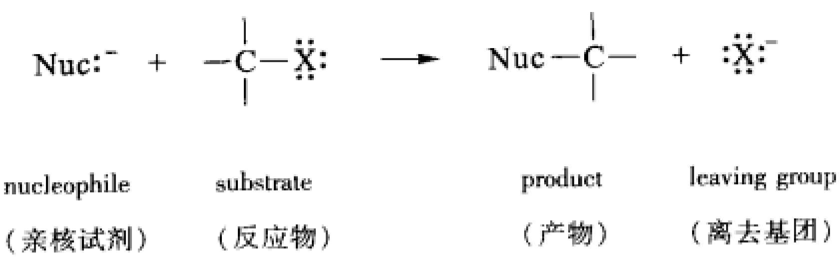
(a) $Na^+\ ^-OCH_2CH_3$

(b) NaCN

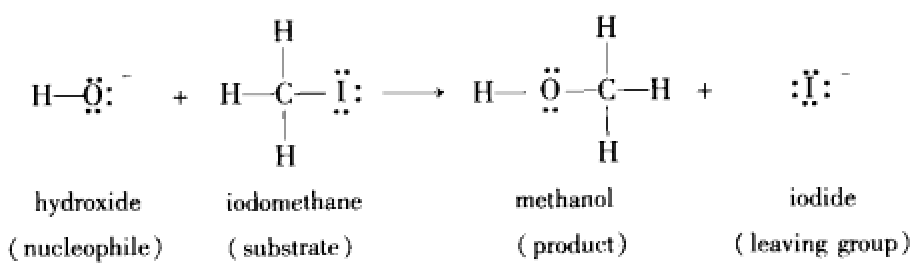
(c) NaOH

7-7 Second-Order Nucleophilic Substitution: The S_N2 Reaction

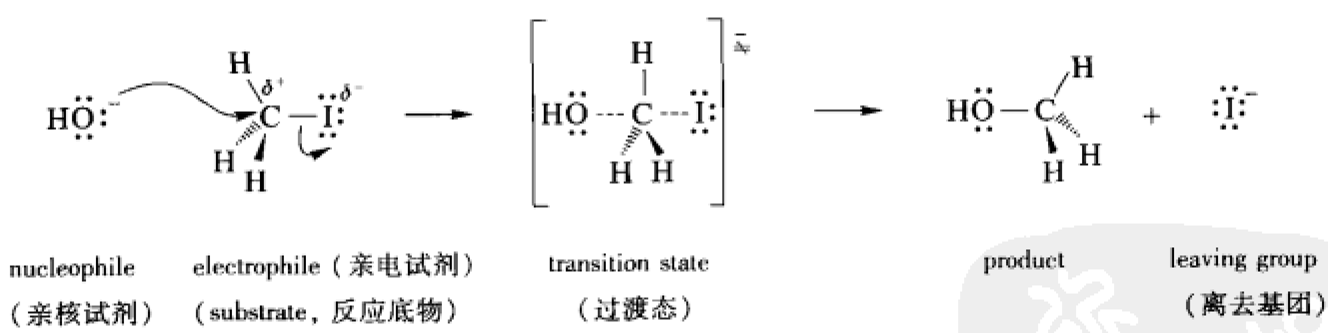
A nucleophilic substitution has the general form



where Nuc:$^-$ is the nucleophile and :X:$^-$ is the leaving halide ion. An example is the reaction of iodomethane (CH_3I) with hydroxide ion. The product is methanol.



Hydroxide ion is a strong **nucleophile** (donor of an electron pair) because the oxygen atom has unshared pairs of electrons and a negative charge. Iodomethane is called the **substrate**, meaning the compound that is attacked by the reagent. The carbon atom of iodomethane is electrophilic because it is bonded to an electronegative iodine atom. Electron density is drawn away from carbon by the halogen atom, giving the carbon atom a partial positive charge. The negative charge of hydroxide ion is attracted to this partial positive charge.



Hydroxide ion attacks the back side of the electrophilic carbon atom, donating a pair of electrons to form a new bond. (In general, nucleophiles are said to attack electrophiles, not the other way around.) Notice that arrows are used to show the movement of electron pairs, from the electron-rich nucleophile to the electron-poor carbon atom of the electrophile. Carbon can accommodate only eight electrons in its valence shell, so the carbon-iodine bond must begin to break as the carbon-oxygen bond begins to form. Iodide ion is the leaving group; it leaves with the pair of electrons that once bonded it to the carbon atom.

This one-step mechanism is supported by kinetic information. One can vary the concentrations of the reactants and observe the effects on the reaction rate (how much methanol is formed per second). The rate is found to double when the concentration of *either* reactant is doubled. The reaction is therefore first order in each of the reactants and second order overall. The rate equation has the following form:

$$\text{rate} = k_r[CH_3I][^-OH]$$

The rate equation is consistent with a mechanism that requires a collision between a molecule of methyl iodide and a hydroxide ion. Both of these species are present in the transition state, and the collision frequency is proportional to both concentrations. The rate constant k_r depends on several factors, including the energy of the transition state and the temperature (Section 5-9).

This one-step nucleophilic substitution is an example of the **S_N2 mechanism.** The abbreviation S_N2 stands for *Substitution*, *Nucleophilic*, *bimolecular.* The term *bimolecular* means that the transition state of the rate-limiting step (the only step in this reaction) involves the collision of *two* molecules. Bimolecular reactions usually have rate equations that are second order overall.

The S_N2 reaction of methyl iodide (iodomet-hane) with hydroxide ion is a **concerted reaction**, taking place in a single step with bonds breaking and forming at the same time. The middle structure is a **transition state**, a point of maximum energy, rather than an intermediate. In this transition state, the bond to the nucleophile (hydroxide) is partially formed, and the bond to the leaving group (iodide) is partially broken. Remember that a transition state is not a discrete molecule that can be isolated; it exists for only an instant.

The reaction-energy diagram for this substitution (Figure 7-2) shows only one transition state and no intermediates between the reactants and the products. The reactants are shown slightly higher in energy than the products because this reaction is known to be exothermic. The transition state is much higher in energy because it involves a five-coordinate carbon atom with two partial bonds.

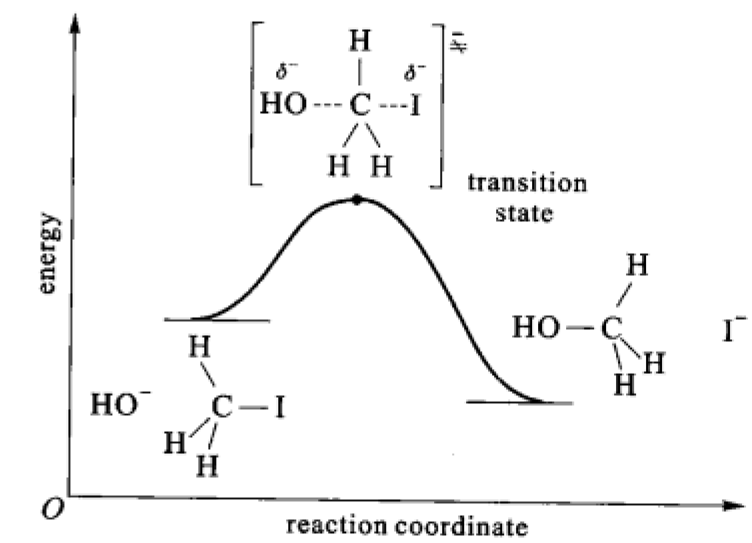
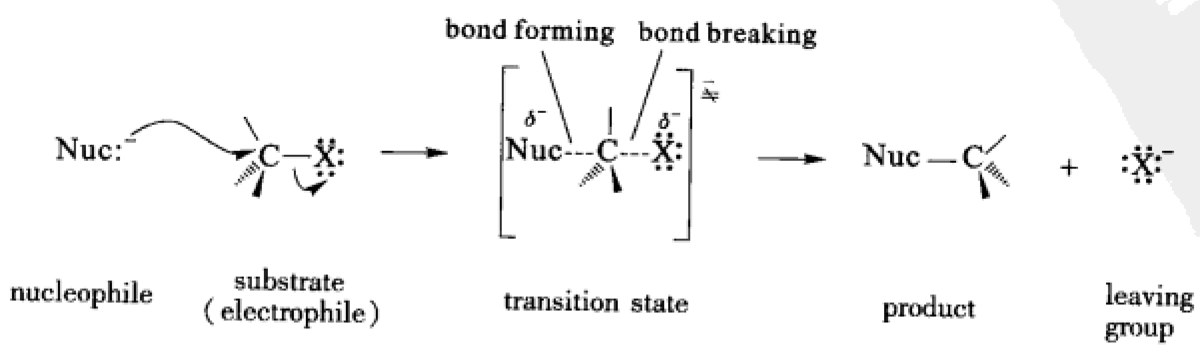


Figure 7-2 The reaction-energy diagram for the S_N2 reaction of methyl iodide with hydroxide shows only one energy maximum; the transition state. There are no intermediates.

The following mechanism shows a general S_N2 reaction. A nucleophile attacks the substrate to give a transition state in which a bond to the nucleophile is forming at the same time as the bond to the leaving group is breaking.

KEY MECHANISM 7-2 The S_N2 Reaction

The S_N2 reaction takes place in a single (concerted) step. A strong nucleophile attacks the electrophilic carbon, forcing the leaving group to leave.



The order of reactivity for substrates is $CH_3X > 1° > 2°$. ($3°$ alkyl halides cannot react by this mechanism.)

PROBLEM 7-6

Under certain conditions, the reaction of 0.5 mol/L 1-bromobutane with 1.0 mol/L sodium methoxide forms 1-methoxybutane at a rate of 0.05 mol/L per second. What would be the rate if 0.1 mol/L 1-bromobutane and 2.0 mol/L $NaOCH_3$ were used?

7-8 Generality of the S_N2 Reaction

Many useful reactions take place by the S_N2 mechanism. The reaction of an alkyl halide, such as methyl iodide, with hydroxide ion gives an alcohol. Other nucleophiles convert alkyl halides to a wide variety of functional groups. The following table summarizes some of the types of compounds that can be formed by nucleophilic displacement of alkyl halides.

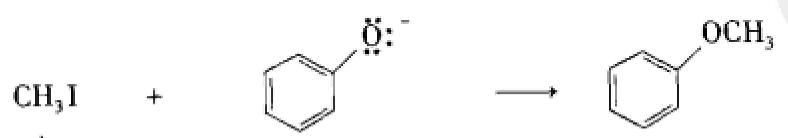
SUMMARY S_N2 Reactions of Alkyl Halides

$$Nuc:^- + R{-}X \longrightarrow Nuc{-}R + X^-$$

Nucleophile		*Product*	*Class of Product*
$R{-}X + {}^-:\ddot{\underset{..}{I}}:$	⟶	$R{-}\ddot{\underset{..}{I}}:$	alkyl halide（卤代烷烃）
$R{-}X + {}^-:\ddot{\underset{..}{O}}H$	⟶	$R{-}\ddot{\underset{..}{O}}H$	alcohol(醇)
$R{-}X + {}^-:\ddot{\underset{..}{O}}R'$	⟶	$R{-}\ddot{\underset{..}{O}}R'$	ether（醚）
$R{-}X + {}^-:\ddot{\underset{..}{S}}H$	⟶	$R{-}\ddot{\underset{..}{S}}H$	thiol(mercaptan)（硫醇）
$R{-}X + {}^-:\ddot{\underset{..}{S}}R'$	⟶	$R{-}\ddot{\underset{..}{S}}R'$	thioether (sulfide)（硫醚）
$R{-}X + {}^-:NH_3$	⟶	$R{-}NH_3^+ X^-$	amine（胺）
$R{-}X + {}^-:\dot{N}{=}\overset{+}{N}{=}\dot{N}:^-$	⟶	$R{-}\dot{N}{=}\overset{+}{N}{=}\dot{N}:^-$	azide（叠氮化物）
$R{-}X + {}^-:C{\equiv}C{-}R'$	⟶	$R{-}C{\equiv}C{-}R'$	alkyne（炔）
$R{-}X + {}^-:C{\equiv}N:$	⟶	$R{-}C{\equiv}N:$	nitrile（腈）
$R{-}X + R'{-}CO\ddot{\underset{..}{O}}:^-$	⟶	$R'{-}COO{-}R$	ester（酯）
$R{-}X + :P(Ph)_3$	⟶	$[R{-}PPh_3]^+\ {}^-X$	phosphonium salt（鏻盐）

Examples

benzyl chloride（苄基氯） hydroxide（氢氧根负离子） benzyl alcohol（苄醇）



iodomethane (methyl iodide) phenoxide(酚氧基负离子) methoxybenzene (methylphenyl ether)

$$CH_3CH_2CH_2CH_2CH_2Br + {}^-:\ddot{\underset{..}{S}}H \longrightarrow CH_3CH_2CH_2CH_2CH_2SH$$

1-bromopentane 1-pentanethiol

$$CH_3CH_2CH_2CH_2Cl + :NH_3 \longrightarrow CH_3CH_2CH_2CH_2NH_2$$

1-chlorobutane (*n*-butyl chloride) + ammonia (excess) → 1-butanamine (*n*-butylamine)

$$CH_3CH_2Br + Na^+ \ ^-:C{\equiv}C{-}H \longrightarrow CH_3CH_2{-}C{\equiv}C{-}H$$

bromoethane (ethyl bromide) + sodium acetylide (乙炔钠) → 1-butyne (ethylacetylene)

$$CH_3CH_2CH_2I + \ ^-:C{\equiv}N \longrightarrow CH_3CH_2CH_2{-}C{\equiv}N$$

1-iodopropane (*n*-propyl iodide) + cyanide (氰基) → butanenitrile (butyronitrile)

Halogen Exchange Reactions The S_N2 reaction provides a useful method for synthesizing alkyl iodides and fluorides, which are more difficult to make than alkyl chlorides and bromides. Halides can be converted to other halides by **halogen exchange reactions**, in which one halide displaces another.

Iodide is a good nucleophile, and many alkyl chlorides react with sodium iodide to give alkyl iodides. Alkyl fluorides are difficult to synthesize directly, and they are often made by treating alkyl chlorides or bromides with KF under conditions that use a crown ether and an aprotic solvent to enhance the normally weak nucleophilicity of the fluoride ion (see Section 7-9).

$$R{-}X + I^- \longrightarrow R{-}I + X^-$$

$$R{-}X + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} R{-}F + KX$$

Examples

$$H_2C{=}CH{-}CH_2Cl + NaI \longrightarrow H_2C{=}CH{-}CH_2I + NaCl$$

allyl chloride → allyl iodide

$$CH_3CH_2Cl + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} CH_3CH_2F + KCl$$

ethyl chloride → ethyl fluoride

PROBLEM 7-7

Show how you would convert 1-chlorobutane into the following compounds.

(a) 1-butanol
(b) 1-fluorobutane
(c) 1-iodobutane
(d) $CH_3{-}(CH_2)_3{-}CN$
(e) $CH_3{-}(CH_2)_3{-}C{\equiv}CH$
(f) $CH_3CH_2{-}O{-}(CH_2)_3{-}CH_3$
(g) $CH_3{-}(CH_2)_3{-}NH_2$

7-9 Factors Affecting S_N2 Reactions: Strength of the Nucleophile

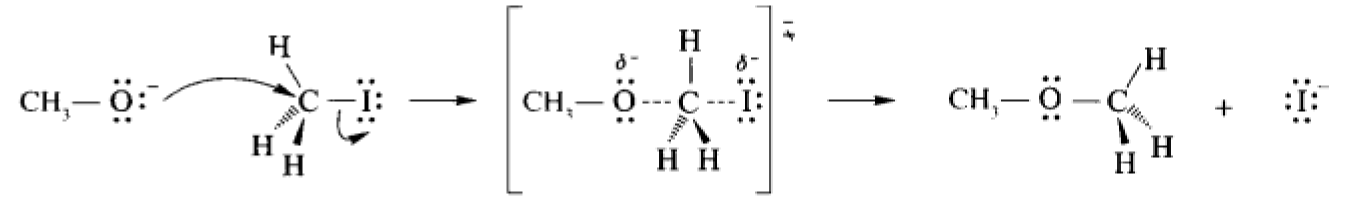
We will use the S_N2 reaction as an example of how we study the properties of the species that participate in the reaction. Both the nucleophile and the substrate (the alkyl halide) are important, as well as the type of solvent used. We begin by considering what makes a good nucleophile.

The nature of the nucleophile strongly affects the rate of the S_N2 reaction. A strong nucleophile is much more effective than a weak one in attacking an electrophilic carbon atom. For example, both methanol (CH_3OH) and methoxide ion (CH_3O^-) have easily shared pairs of nonbonding electrons, but methoxide ion reacts with electrophiles in the S_N2 reaction about 1 million times faster than methanol. It is generally true that a species

with a negative charge is a stronger nucleophile than a similar, neutral species.

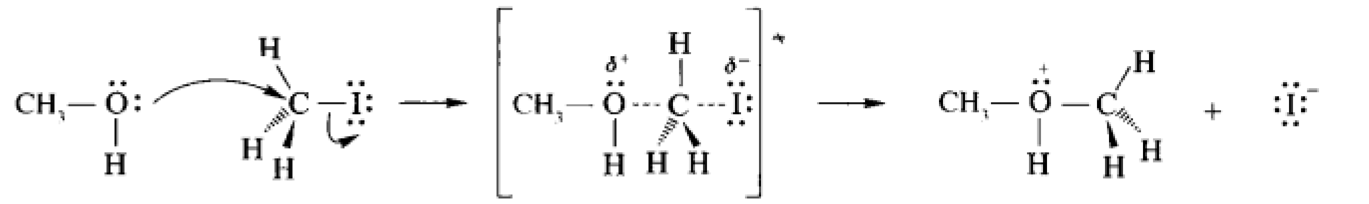
Methoxide ion has nonbonding electrons that are readily available for bonding. In the transition state, the negative charge is shared by the oxygen of methoxide ion and by the halide leaving group. Methanol, however, has no negative charge; the transition state has a partial negative charge on the halide but a partial positive charge on the methanol oxygen atom. We can generalize the case of methanol and the methoxide ion to say that:

A base is always a stronger nucleophile than its conjugate acid.



conjugate base
(stronger nucleophile)

lower E_a



conjugate acid
(weaker nucleophile)

higher E_a

We might be tempted to say that methoxide is a much better nucleophile because it is much more basic. This would be a mistake because basicity and nucleophilicity are different properties. **Basicity** is defined by the *equilibrium constant* for abstracting a *proton*. **Nucleophilicity** is defined by the *rate* of attack on an electrophilic *carbon atom*. In both cases, the nucleophile (or base) forms a new bond. If the new bond is to a proton, it has reacted as a **base**; if the new bond is to carbon, it has reacted as a **nucleophile.** Predicting which way a species will react may be difficult; most (but not all) good nucleophiles are also strong bases, and vice versa.

Basicity

$$B:^- + H-A \overset{K_{eq}}{\rightleftharpoons} B-H + A:^-$$

Nucleophilicity

$$B:^- + -\overset{|}{\underset{|}{C}}-X \xrightarrow{k_r} B-\overset{|}{\underset{|}{C}}- + X:^-$$

Table 7-3 lists some common nucleophiles in decreasing order of their nucleophilicity in common solvents such as water and alcohols. The strength of nucleophiles shows three major trends:

TABLE 7-3 Some Common Nucleophiles, Listed in Decreasing Order of Nucleophilicity in Hydroxylic Solvents Such as Water and Alcohols

strong nucleophiles	$(CH_3CH_2)_3P:$	moderate nucleophiles	$:\ddot{Br}:^-$
	$^-:\ddot{S}-H$		$:NH_3$
	$:\ddot{I}:^-$		$CH_3-\ddot{S}-CH_3$
	$(CH_3CH_2)_2\ddot{N}H$		$:\ddot{Cl}:^-$
	$^-:C\equiv N$		$CH_3C(=O)-\ddot{O}:^-$
	$(CH_3CH_2)_3N:$		
	$H-\ddot{O}:^-$	weak nucleophiles	$:\ddot{F}:^-$

Continue

$CH_3—\ddot{O}:^-$	$H—\ddot{O}—H$ $CH_3—\ddot{O}—H$

SUMMARY Trends in Nucleophilicity

1. A species with a negative charge is a stronger nucleophile than a similar neutral species. In particular, a base is a stronger nucleophile than its conjugate acid.

$$^-:\ddot{O}H > H_2\ddot{O}: \qquad ^-:\ddot{S}H > H_2\ddot{S}: \qquad ^-:\ddot{N}H_2 > :NH_3$$

2. Nucleophilicity decreases from left to right in the periodic table, following the increase in electronegativity from left to right The more electronegative elements have more tightly held nonbonding electrons that are less reactive toward forming new bonds.

$$^-:\ddot{O}H > :\ddot{F}:^- \qquad :NH_3 > H_2\ddot{O}: \qquad (CH_3CH_2)_3P: > (CH_3CH_2)_2\ddot{S}:$$

3. Nucleophilicity increases down the periodic table, following the increase in size and polarizability.

$$:\ddot{I}:^- > :\ddot{Br}:^- > :\ddot{Cl}:^- > :\ddot{F}:^- \qquad ^-:\ddot{S}eH > ^-:\ddot{S}H > ^-:\ddot{O}H \qquad (CH_3CH_2)_3P: > (CH_3CH_2)_3N:$$

The third trend (size and polarizability) reflects an atom's ability to engage in partial bonding as it begins to attack an electrophilic carbon atom. As we go down a column in the periodic table, the atoms become larger, with more electrons at a greater distance from the nucleus, The electrons are more loosely held, and the atom is more **polarizable**: Its electrons can move more freely toward a positive charge, resulting in stronger bonding in the transition state. The increased mobility of its electrons enhances the atom's ability to begin to form a bond at a relatively long distance.

Figure 7-3 illustrates this polarizability effect by comparing the attack of iodide ion and fluoride ion on a methyl halide. The outer shell of the fluoride ion is the second shell. These electrons are tightly held, close to

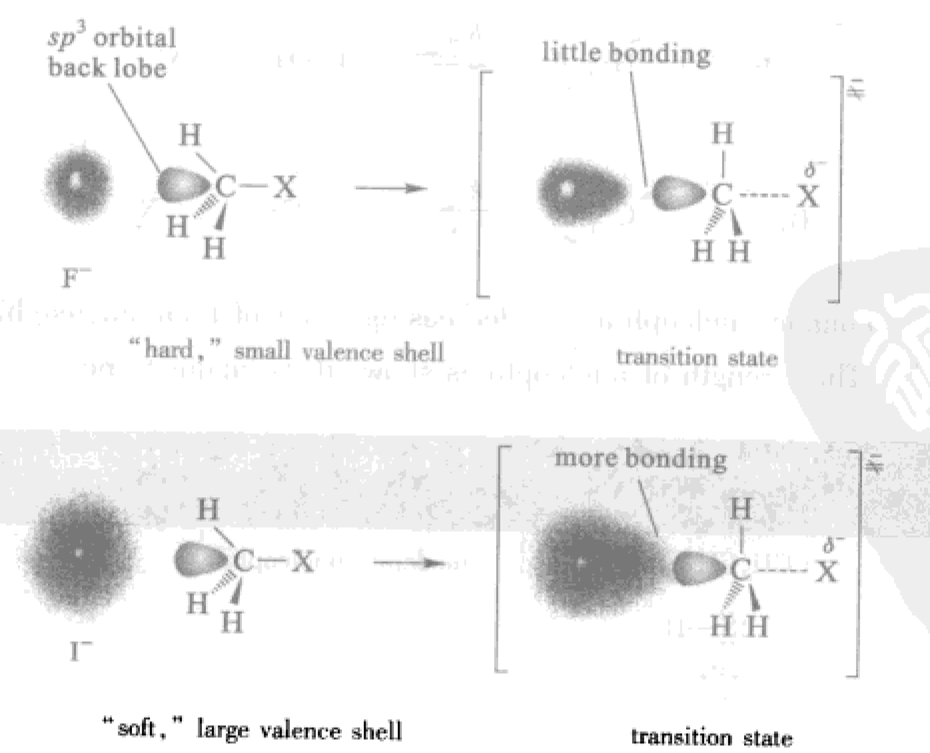
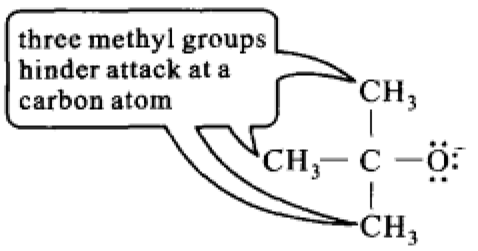


Figure 7-3 Comparison of fluoride ion and iodide ion as nucleophiles in the S_N2 reaction. Fluoride has tightly bound electrons that cannot begin to form a C—F bond until the atoms are close together. Iodide has more loosely bound outer electrons that begin bonding earlier in the reaction.

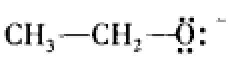
the nucleus. Fluoride is a "hard" (low-polarizability) nucleophile, and its nucleus must approach the carbon nucleus quite closely before the electrons can begin to overlap and form a bond. In the transition state, there is little bonding between fluorine and carbon. In contrast, the outer shell of the iodide ion is the fifth shell, These electrons are loosely held, making the iodide ion a "soft" (high-polarizability) nucleophile. The outer electrons begin to shift and overlap with the carbon atom from farther away. There is a great deal of bonding between iodine and carbon in the transition state, which lo-wers the energy of the transition state.

7-9A Steric Effects on Nucleophilicity

To serve as a nucleophile, an ion or molecule must get in close to a carbon atom to attack it. Bulky groups on the nucleophile hinder this close approach, and they slow the reaction rate. For example, the *t*-butoxide ion is a stronger *base* (for abstracting protons) than ethoxide ion, but *t*-butoxide ion has three methyl groups that hinder any close approach to a carbon atom. Therefore, ethoxide ion is a stronger nucleophile than *t*-butoxide ion. When bulky groups interfere with a reaction by virtue of their size, we call the effect **steric hindrance.**



t-butoxide (hindered)(叔丁氧基负离子)
stronger base, yet weaker nucleophile



ethoxide (unhindered)(乙氧基负离子)
weaker base, yet stronger nucleophile

Steric hindrance has little effect on *basicity* because basicity involves attack on an unhindered proton. When a *nucleophilic* attack at a carbon atom is involved, however, a bulky base cannot approach the carbon atom so easily. Most bases are also nucleophiles, capable of attacking either a proton or an electrophilic carbon atom. If we want a species to act as a base, we use a bulky reagent like *t*-butoxide ion. If we want it to react as a nucleophile, we use a less hindered reagent, like ethoxide.

PROBLEM 7-8

For each pair, predict the stronger nucleophile in the S_N2 reaction (using an alcohol as the solvent). Explain your prediction.

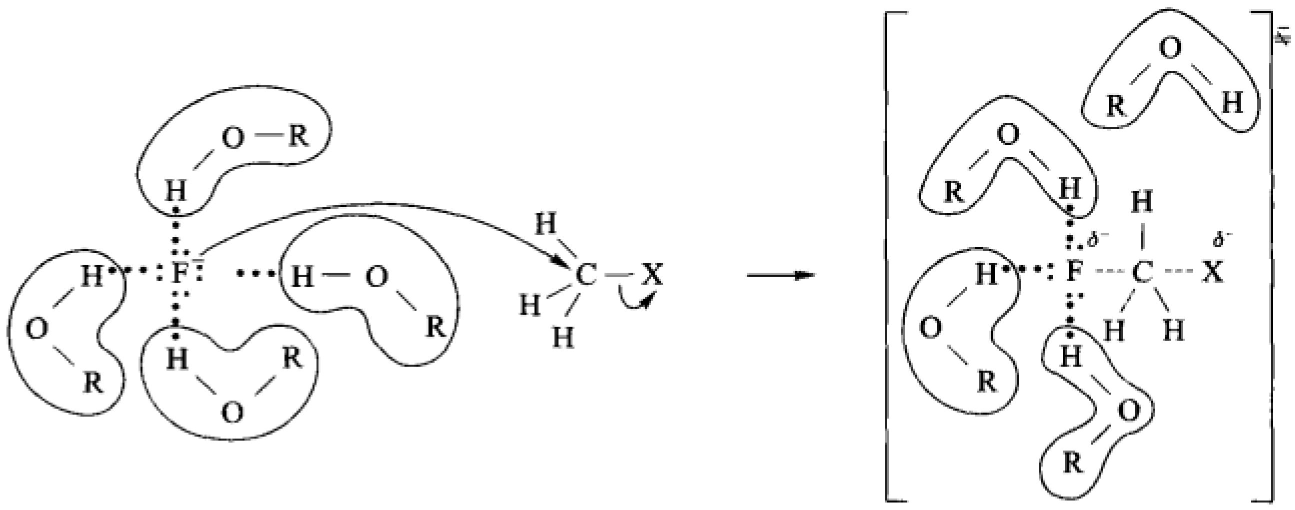
(a) $(CH_3CH_2)_3N$ or $(CH_3CH_2)_2NH$
(b) $(CH_3)_2O$ or $(CH_3)_2S$
(c) NH_3 or PH_3
(d) CH_3S^- or H_2S
(e) $(CH_3)_3N$ or $(CH_3)_2O$
(f) CH_3S^- or CH_3OH
(g) $(CH_3)_2CHO^-$ or $CH_3CH_2CH_2O^-$
(h) I^- or Cl^-

7-9B Solvent Effects on Nucleophilicity

Another factor in the nucleophilicity of these ions is their solvation, particularly in protic solvents. A **protic solvent** is one that has acidic protons, usually in the form of O—H or N—H groups. These groups form hydrogen bonds to negatively charged nucleophiles. Protic solvents, especially alcohols, are convenient solvents for nucle-

ophilic substitutions because the reagents (alkyl halides, nucleophiles, etc.) tend to be quite soluble.

Small anions are solvated more strongly than large anions in a protic solvent because the solvent approaches a small anion more closely and forms stronger hydrogen bonds. When an anion reacts as a nucleophile, energy is required to "strip off" some of the solvent molecules, breaking some of the hydrogen bonds that stabilized the solvated anion. More energy is required to strip off solvent from a small, strongly solvated ion such as fluoride than from a large, diffuse, less strongly solvated ion like iodide.



solvent partially stripped off in the transition state

The enhanced solvation of smaller anions in protic solvents, requiring more energy to strip off their solvent molecules, reduces their nucleophilicity. This trend reinforces the trend in polarizability: The polarizability increases with increasing atomic number, and the solvation energy (in protic solvents) decreases with increasing atomic number. Therefore, nucleophilicity (in protic solvents) generally increases down a column in the periodic table, as long as we compare similar species with similar charges.

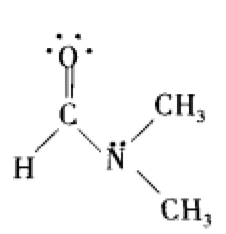
In contrast with protic solvents, **aprotic solvents** (solvents without O—H or N—H groups) enhance the nucleophilicity of anions. An anion is more reactive in an aprotic solvent because it is not so strongly solvated. There are no hydrogen bonds to be broken when solvent must make way for the nucleophile to approach an electrophilic carbon atom. The relatively weak solvating ability of aprotic solvents is also a disadvantage: Most polar, ionic reagents are not soluble in simple aprotic solvents such as alkanes.

Polar aprotic solvents have strong dipole moments to enhance solubility, yet they have no O—H or N—H groups to form hydrogen bonds with anions. Examples of useful polar aprotic solvents are acetonitrile, dimethylformamide, and acetone, We can add specific solvating reagents to enhance solubility without affecting the reactivity of the nucleophile. For example, the "crown ether" 18-crown-6 solvates potassium ions. Using the potassium salt of a nucleophile and solvating the potassium ions causes the nucleophilic anion to be dragged along into solution.

CH_3—C≡N:

acetonitrile

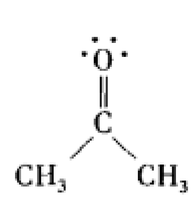
(乙腈)



dimethylformamide

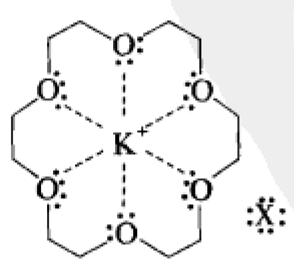
(DMF)

(二甲基甲酰胺)



acetone

(丙酮)

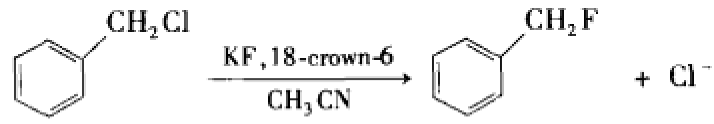


18-crown-6

solvates K^+ ions

[18-冠(醚)-6]

The following example shows how fluoride ion, normally a poor nucleophile in hydroxylic (protic) solvents, can be a good nucleophile in an aprotic solvent, Although KF is not very soluble in acetonitrile, 18-crown-6 solvates the potassium ions, and the poorly solvated (and therefore nucleophilic) fluoride ion follows.



7−10 Reactivity of the Substrate in S_N 2 Reactions

Just as the nucleophile is important in the S_N2 reaction, the structure of the alkyl halide is equally important. We will often refer to the alkyl halide as the **substrate**: literally, the compound that is being attacked by the reagent. Besides alkyl halides, a variety of other types of compounds serve as substrates in S_N2 reactions. To be a good substrate for S_N2 attack by a nucleophile, a molecule must have an electrophilic carbon atom with a good leaving group, and that carbon atom must not be too sterically hindered for a nucleophile to attack.

7−10A Leaving-Group Effects on the Substrate

A leaving group serves two purposes in the S_N2 reaction: It polarizes the C—X bond—making the carbon atom electrophilic—and it leaves with the pair of electrons that once bonded it to the electrophilic carbon atom. To fill these roles, a good leaving group should be

1. electron withdrawing, to polarize the carbon atom,
2. stable (not a strong base) once it has left,
3. polarizable, to stabilize the transition state.

1. The leaving group must be *electron withdrawing* to create a partial positive charge on the carbon atom, making the carbon electrophilic. An electron-withdrawing leaving group also stabilizes the negatively charged transition state. Halogen atoms are strongly electronegative, so alkyl halides are common substrates for S_N2 reactions. Oxygen, nitrogen, and sulfur also form strongly polarized bonds with carbon; given the right substituents, they can form the basis for excellent leaving groups.

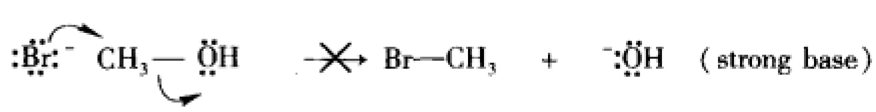
Strongly polarized

$$\overset{\longmapsto}{C—X}\ (X = \text{halogen}) \qquad \overset{\longmapsto}{C—O} \qquad \overset{\longmapsto}{C—N} \qquad \overset{\longmapsto}{C—S}$$

2. The leaving group must be *stable* once it has left with the pair of electrons that bonded it to carbon. A stable leaving group is needed for favorable energetics. The leaving group is leaving in the transition state; a reactive leaving group would raise the energy of the transition state, slowing the reaction. Also, the energy of the leaving group is reflected in the energy of the products. A reactive leaving group would raise the energy of the products, driving the equilibrium toward the reactants.

Good leaving groups should be *weak bases*; therefore, they are the conjugate bases of strong acids. The hydrohalic acids HCl, HBr, and HI are strong, and their conjugates (Cl^-, Br^-, and I^-) are all weak bases. Other weak bases, such as sulfate ions, sulfonate ions, and phosphate ions, can also serve as good leaving groups. Table 7−4 lists examples of good leaving groups.

Hydroxide ion, alkoxide ions, and other strong bases are poor leaving groups for S_N2 reactions. For example, the—OH group of an alcohol is a poor leaving group because it would have to leave as hydro-xide ion.



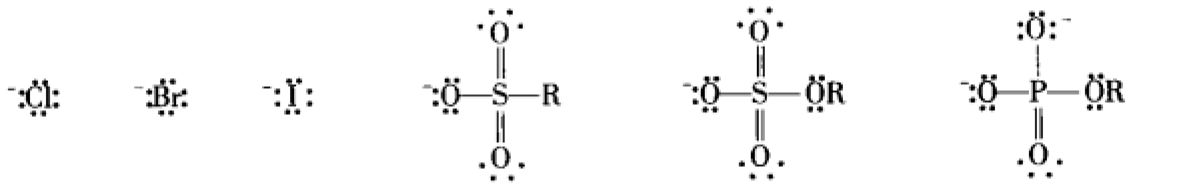
Ions that are strong bases and poor leaving groups:

$^-$:ÖH	$^-$:ÖR	$^-$:N̈H_2
hydroxide(羟基)	alkoxide(烷氧基)	amide(氨基)

Table 7 − 4 also lists some neutral molecules that can be good leaving groups. A neutral molecule often serves as the leaving group from a *positively charged* species.

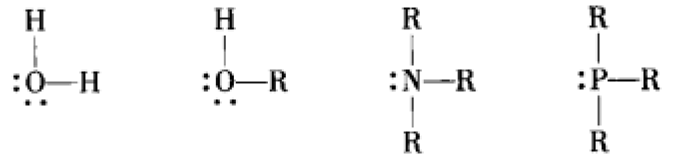
TABLE 7 − 4 Weak Bases That Are Common Leaving Groups

Ions:



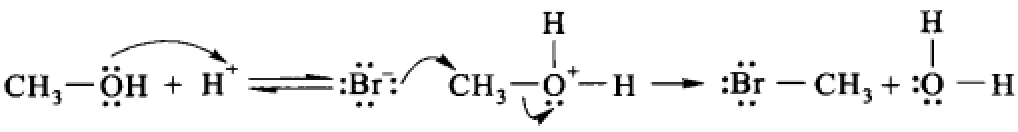
halides(卤负离子) sulfonate(磺酸根) sulfate(硫酸根) phosphate(磷酸根)

Neutral molecules:



water alcohols amines phosphines

For example, if an alcohol is placed in an acidic solution, the hydroxyl group is protonated. Water then serves as the leaving group. Note that the need to protonate the alcohol (requiring acid) limits the choice of nucleophiles to those few that are weak bases, such as bromide and iodide. A strongly basic nucleophile would become protonated in acid.



protonated alcohol (质子化醇) water

3. Finally, a good leaving group should be *polarizable*, to maintain partial bonding with the carbon atom in the transition state. This bonding helps stabilize the transition state and reduce the activation energy. The departure of a leaving group is much like the attack of a nucleophile, except that the bond is breaking rather than forming. Polarizable nucleophiles and polarizable leaving groups both stabilize the transition state by engaging in more bonding at a longer distance. Iodide ion, one of the most polarizable ions, is both a good nucleophile and a good leaving group. In contrast, fluoride ion is a small, "hard" ion. Fluoride is both a poor nucleophile (in protic solvents) and a poor leaving group in S_N2 reactions.

PROBLEM 7−9

When dimethyl ether (CH_3—O—CH_3) is treated with concentrated HBr, the initial products are CH_3Br and CH_3OH. Propose a mechanism to account for this reaction.

7-10B Steric Effects on the Substrate

Different alkyl halides undergo S_N2 reactions at vastly different rates. The structure of the substrate is the most important factor in its reactivity toward S_N2 displacement. The reaction goes rapidly with methyl halides and with most primary substrates. It is more sluggish with secondary halides. Tertiary halides fail to react at all by the S_N2 mechanism. Table7-5 shows the effect of alkyl substitution on the rate of S_N2 displacements.

For simple alkyl halides, the relative rates for S_N2 displacement are

$$\text{Relative rates for } S_N2: \quad CH_3X > 1° > 2° > 3°$$

The physical explanation for this order of reactivity is suggested by the information in Table 7-5. All the slow-reacting compounds have one property in common: The back side of the electrophilic carbon atom is crowded by the presence of bulky groups. Tertiary halides are more hindered than secondary halides, which are more hindered than primary halides. Even a bulky primary halide (like neopentyl bromide) undergoes S_N2 reaction at a rate similar to that of a tertiary halide. The relative rates show that it is the bulk of the alkyl groups, rather than an electronic effect, that hinders the reactivity of bulky alkyl halides in the S_N2 displacement.

TABLE 7-5 Effect of Substituents on the Rates of S_N2 Reactions

Class of Halide	Example	Relative Rate
methyl	CH_3—Br	>1000
primary (1°)	CH_3CH_2—Br	50
secondary (2°)	$(CH_3)_2CH$—Br	1
tertiary (3°)	$(CH_3)_3C$—Br	<0.001
n-butyl (1°)	$CH_3CH_2CH_2CH_2$—Br	20
isobutyl(1°)	$(CH_3)_2CHCH_2$—Br	2
neopentyl(1°)	$(CH_3)_3CCH_2$—Br	0.0005

Note: Two or three alkyl groups, or even a single bulky alkyl group, slow the reaction rate. The rates listed are compared to the secondary case (isopropyl bromide), assigned a relative rate of 1.

This effect on the rate is another example of **steric hindrance.** When the nucleophile approaches the back side of the electrophilic carbon atom, it must come within bonding distance of the back lobe of the C—X sp^3 orbital. If there are two alkyl groups bonded to the carbon atom, this process is difficult. Three alkyl groups make it impossible. Just one alkyl group can produce a large amount of steric hindrance if it is unusually bulky, like the *t*-butyl group of neopentyl bromide.

Figure 7-4 shows the S_N2 reaction of hydroxide ion with ethyl bromide (1°), isopropyl bromide (2°), and *t*-butyl bromide (3°). The nucleophile can easily approach the electrophilic carbon atom of ethyl bromide. In isopropyl bromide, the approach is hindered, but still possible. In contrast, S_N2 approach to the tertiary carbon of *t*-butyl bromide is impossible because of the steric hindrance of the three methyl groups. Make models of ethyl bromide, isopropyl bromide, and *t*-butyl bromide, and compare the ease of bringing in an atom for a back-side attack.

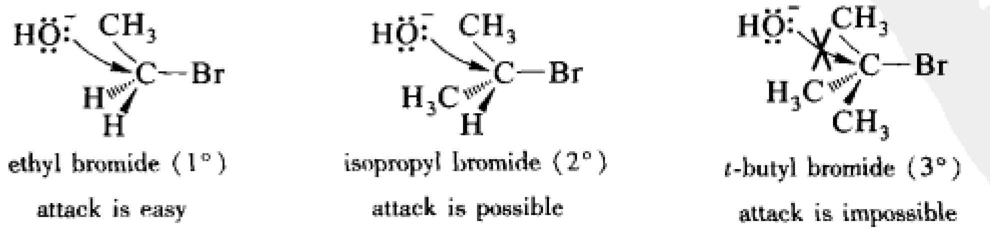


Figure 7-4 S_N2 attack on a simple primary alkyl halide is unhindered. Attack on a secondary halide is hindered, and attack on a tertiary halide is impossible.

PROBLEM 7−10

Rank the following compounds in decreasing order of their reactivity toward the S_N2 reaction with sodium ethoxide ($Na^+ \, ^-OCH_2CH_3$) in ethanol.

methyl chloride	*t*-butyl iodide	neopentyl bromide
isopropyl bromide	methyl iodide	ethyl chloride

7−11 Stereochemistry of the S_N2 Reaction

As we have seen, the S_N2 reaction requires attack by a nucleophile on the back side of an electrophilic carbon atom (Figure 7−5). A carbon atom can have only four filled bonding orbitals (an octet), so the leaving group must leave as the nucleophile bonds to the carbon atom. The nucleophile's electrons insert into the back lobe of carbon's sp^3 hybrid orbital in its antibonding combination with the orbital of the leaving group (because the bonding MO is already filled). These electrons in the antibonding MO help to weaken the C—Br bond as bromine leaves. The transition state shows partial bonding to both the nucleophile and the leaving group.

Back-side attack literally turns the tetrahedron of the carbon atom inside out, like an umbrella caught by the wind (Figure 7−5). In the product, the nucleophile assumes a stereochemical position opposite the position the leaving group originally occupied. We call this result an **inversion of configuration** at the carbon atom.

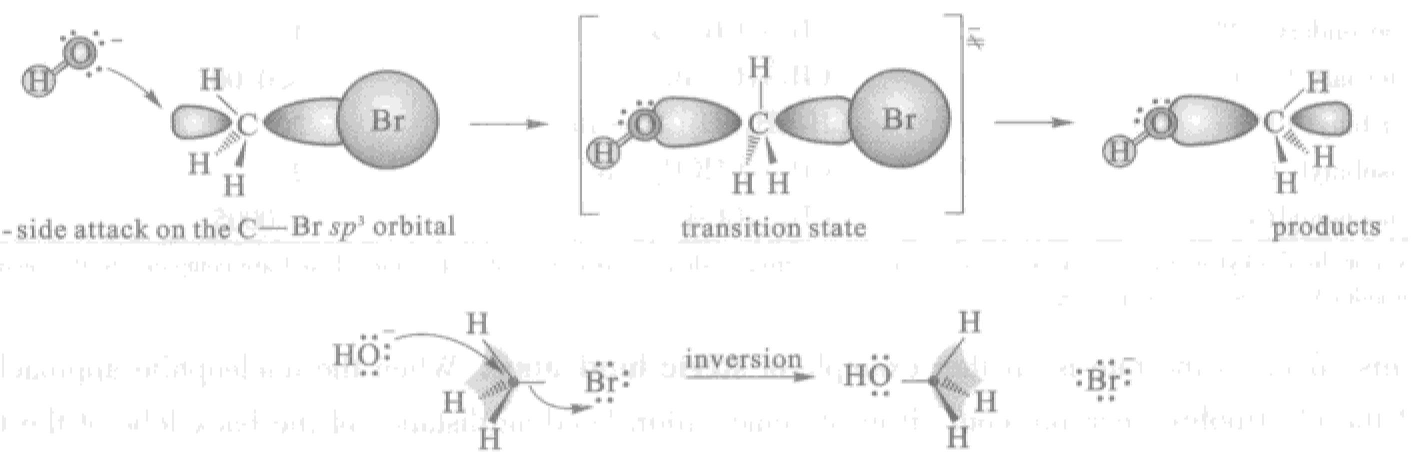
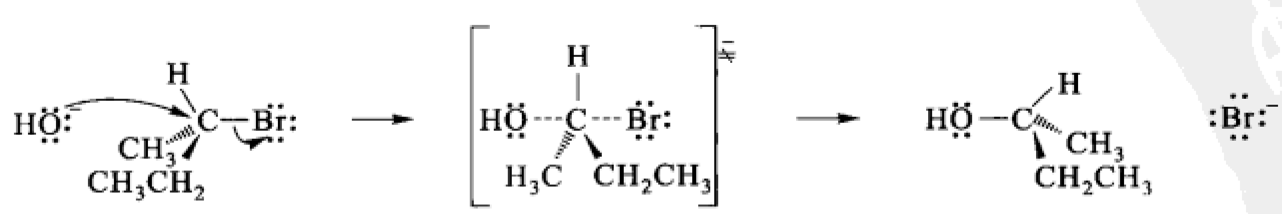


Figure 7−5 Back-side attack in the S_N2 reaction. The S_N2 reaction takes place through nucleophilic attack on the back lobe of carbon's sp^3 hybrid orbital. This back-side attack inverts the carbon atom's tetrahedron, like the wind inverts an umbrella.

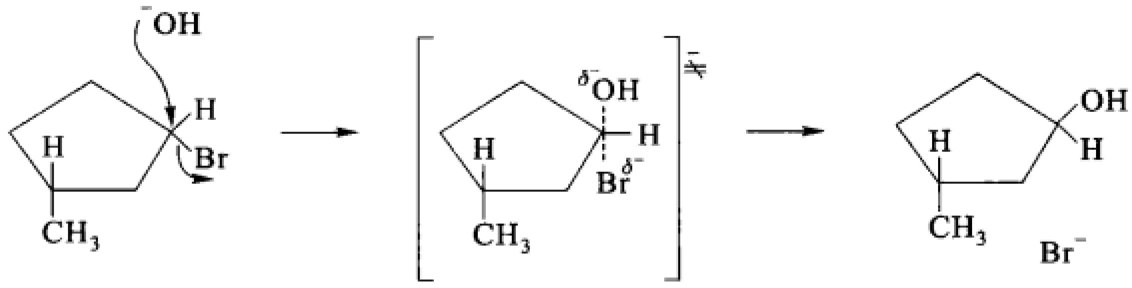
In the case of an asymmetric carbon atom, back-side attack gives the opposite configuration of the carbon atom as the following example. The S_N2 displacement is the most common example of a **Walden inversion**, a step (in a reaction sequence) where an asymmetric carbon atom undergoes inversion of configuration. In the 1890s, Paul Walden, of the University of Tübingen (Germany), was one of the first to study reactions giving inversion of configuration.

Example



(*S*)-2-bromobutane (*R*)-2-butanol

In some cases, inversion of configuration is readily apparent. For example, when *cis*-1-bromo-3-methylcyclopentane undergoes S_N2 displacement by hydroxide ion, inversion of configuration gives *trans*-3-methylcyclopentanol.



cis-1-bromo-3-methylcyclopentane　　transition state　　*trans*-3-methylcyclopentanol

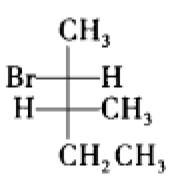
The S_N2 displacement is a good example of a **stereospecific reaction**: one in which different stereoisomers react to give different stereoisomers of the product. To study the mechanism of a nucleophilic substitution, we often look at the product to see if the reaction is stereospecific, with inversion of configuration. If it is, the S_N2 mechanism is a good possibility, especially if the reaction kinetics are second order. In many cases (no asymmetric carbon or ring, for example) it is impossible to determine whether inversion has occurred. In these cases, we use kinetics and other evidence to help determine the reaction mechanism.

PROBLEM 7-11

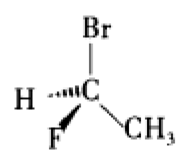
Draw a perspective structure or a Fischer projection for the products of the following S_N2 reactions.

(a) *trans*-1-bromo-3-methylcyclopentane + KOH

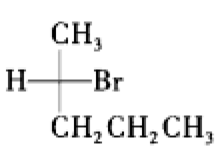
(b) (*R*)-2-bromopentane + KCN

(c) 

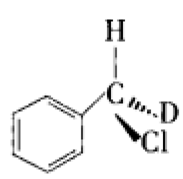
+ NaI $\xrightarrow{\text{acetone}}$

(d) 

+ NaSH

(e) 

+ $NaOCH_3$ $\xrightarrow{CH_3OH}$

(f) 

+ NH_3

PROBLEM 7-12

Under appropriate conditions, (*S*)-1-bromo-1-fluoroethane reacts with sodium methoxide to give pure (*S*)-1-fluoro-1-methoxyethane.

$$\underset{(S)}{CH_3CHBrF} + NaOCH_3 \longrightarrow \underset{(S)}{CH_3CHFOCH_3} + NaBr$$

(a) Why is bromide rather than fluoride replaced?

(b) Draw perspective structures (as shown on the previous page for 2-bromobutane) for the starting material, the transition state, and the product.

(c) Does the product show retention or inversion of configuration?

(d) Is this result consistent with reaction by the S_N2 mechanism?

7-12 First-Order Nucleophilic Substitution: The S_N1 Reaction

When *t*-butyl bromide is placed in boiling methanol, methyl *t*-butyl ether can be isolated from the reaction mixture. Because this reaction takes place with the solvent acting as the nucleophile, it is called a **solvolysis** (*solvo* for "solvent," plus *lysis*, meaning "cleavage").

$$\underset{t\text{-butyl bromide}}{(CH_3)_3C{-}Br} + \underset{\text{methanol}}{CH_3{-}OH} \xrightarrow{\text{boil}} \underset{\substack{\text{methyl } t\text{-butyl ether} \\ \text{(甲基叔丁基醚)}}}{(CH_3)_3C{-}O{-}CH_3} + HBr$$

This solvolysis is a substitution because methoxide has replaced bromide on the *t*-butyl group. It does not go through the S_N2 mechanism, however. The S_N2 requires a strong nucleophile and a substrate that is not too hindered. Methanol is a weak nucleophile, and *t*-butyl bromide is a hindered tertiary halide—a poor S_N2 substrate.

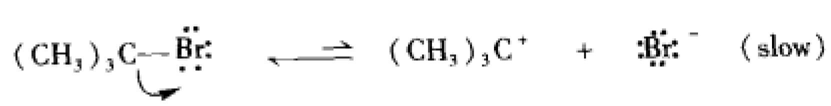
If this substitution cannot go by the S_N2 mechanism, what kind of mechanism might be involved? An important clue is kinetic: Its rate does not depend on the concentration of methanol, the nucleophile. The rate depends only on the concentration of the substrate, *t*-butyl bromide.

$$\text{rate} = k_r[(CH_3)_3C{-}Br]$$

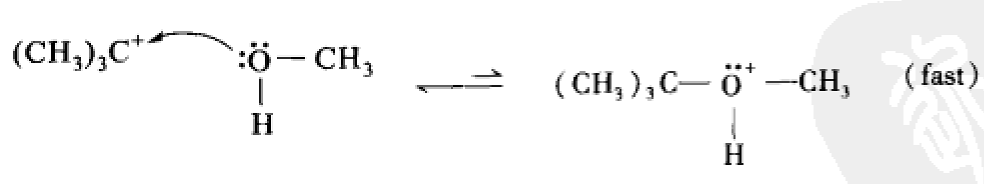
This rate equation is first order overall: first order in the concentration of the alkyl halide and zeroth order in the concentration of the nucleophile. Because the rate does not depend on the concentration of the nucleophile, we infer that the nucleophile is not present in the transition state of the rate-limiting step. The nucleophile must react *after* the slow step.

This type of substitution is called the **S_N1 reaction**, for *Substitution*, *Nucleophilic*, *unimolecular*. The term *unimolecular* means there is only one molecule involved in the transition state of the rate-limiting step. The mechanism of the S_N1 reaction of *t*-butyl bromide with methanol is shown here. Ionization of the alkyl halide (first step) is the rate-limiting step.

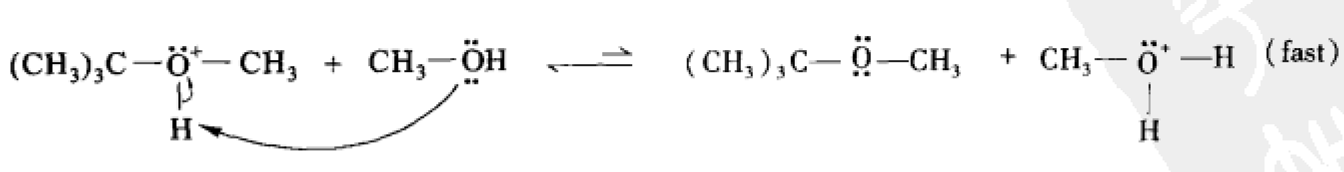
Step 1: Formation of carbocation (rate limiting)



Step 2: Nucleophilic attack on the carbocation



Final Step: Loss of proton to solvent



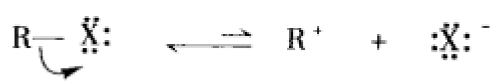
The S_N1 mechanism is a multistep process. The first step is a slow ionization to form a carbocation. The second step is a fast attack on the carbocation by a nucleophile. The carbocation is a strong electrophile; it reacts very fast with nucleophiles, including weak nucleophiles. The nucleophile is usually weak, because a strong nu-

cleophile would be more likely to attack the substrate and force some kind of second-order reaction. If the nucleophile is an uncharged molecule like water or an alcohol, the positively charged product must lose a proton to give the final uncharged product. The general mechanism for the S_N1 reaction is summarized in the Key Mechanism box.

KEY MECHANISM 7-3 **The S_N1 Reaction**

The S_N1 reaction involves a two-step mechanism. A slow ionization gives a carbocation that reacts quickly with a (usually weak) nucleophile. Reactivity: 3° > 2° > 1°.

Step 1. Formation of the carbocation (rate-limiting).



Step 2. Nucleophilic attack on the carbocation (fast).

If the nucleophile is water or an alcohol, a third step is needed to deprotonate the product.

PROBLEM 7-13

Propose an S_N1 mechanism for the solvolysis of 3-bromo-2,3-dimethylpentane in ethanol.

The reaction-energy diagram of the S_N1 reaction (Figure 7-6) shows why the rate does not depend on the strength or concentration of the nucleophile. The ionization (first step) is highly endothermic, and its large activation energy determines the overall reaction rate. The nucleophilic attack (second step) is strongly exothermic, with a lower-energy transition state. In effect, a nucleophile reacts with the carbocation almost as soon as it forms.

The reaction-energy diagrams of the S_N1 mechanism and the S_N2 mechanism are compared in Figure 7-6. The S_N1 has a true intermediate, the carbocation. The intermediate appears as a relative minimum (a low point)

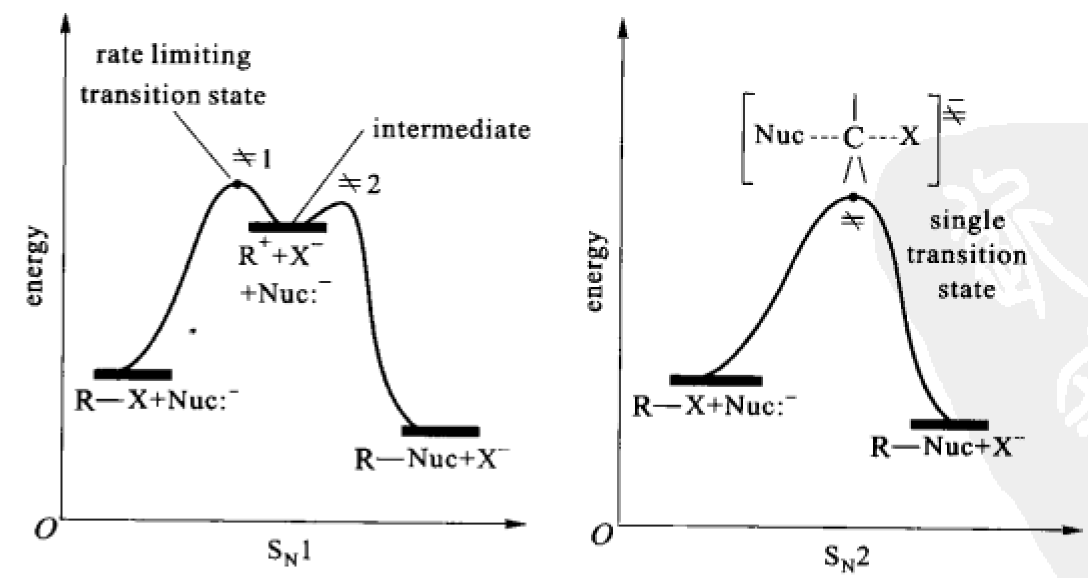


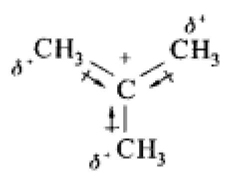
Figure 7-6 Reaction-energy diagrams of the S_N1 and S_N2 reactions. The S_N1 is a two-step mechanism with two transition states (≠1 and ≠2) and a carbocation intermediate. The S_N2 has only one transition state and no intermediate.

in the reaction-energy diagram. Reagents and conditions that favor formation of the carbocation (the slow step) accelerate the S_N1 reaction; reagents and conditions that hinder its formation retard the reaction.

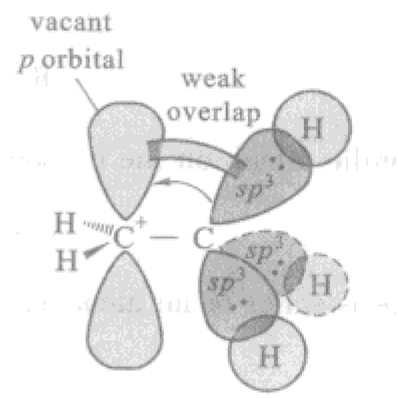
7-12A Substituent Effects

The rate-limiting step of the S_N1 reaction is ionization to form a carbocation, a strongly endothermic process. The transition state resembles the carbocation (Hammond postulate, Section 5-14); consequently, rates of S_N1 reactions depend strongly on carbocation stability. In Section 5-16A, we saw that alkyl groups stabilize carbocations by donating electrons through sigma bonds (the *inductive effect*) and through overlap of filled orbitals with the empty p orbital of the carbocation (*hyperconjugation*). Highly substitued carbocations are therefore more stable.

carbocation stability: $3° > 2° > 1° > {}^{+}CH_3$



inductive effect
(诱导效应)



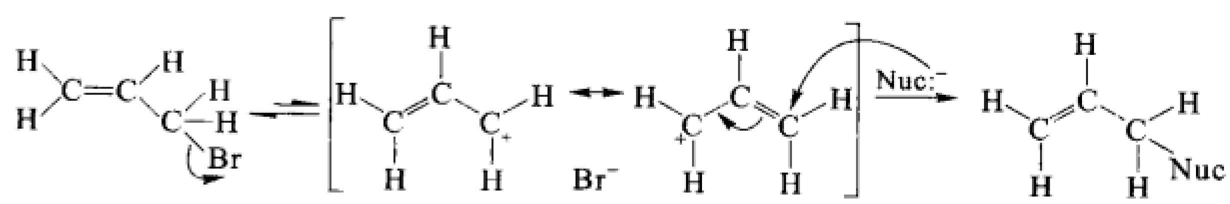
carbocation alkyl group
hyperconjugation
(超共轭)

Reactivity toward S_N1 substitution mechanisms follows the stability of carbocations:

S_N1 reactivity: $3° > 2° > 1° > CH_3X$

This order is *opposite* that of the S_N2 reaction. Alkyl groups hinder the S_N2 by blocking attack of the strong nucleophile, but alkyl groups enhance the S_N1 by stabilizing the carbocation intermediate.

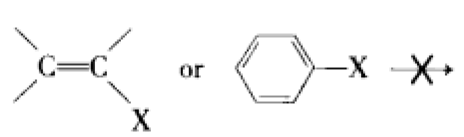
Resonance stabilization of the carbocation can also promote the S_N1 reaction. For example, allyl bromide is a primary halide, but it undergoes the S_N1 reaction about as fast as a secondary halide. The carbocation formed by ionization is resonance stabilized, with the positive charge spread equally over two carbon atoms.



allyl bromide

resonance-stabilized carbocation
(共振稳定化碳正离子)

Vinyl and aryl halides generally do not undergo S_N1 or S_N2 reactions. An S_N1 reaction would require ionization to form a vinyl or aryl cation, either of which is less stable than most alkyl carbocations. An S_N2 reaction would require back-side attack by the nucleophile, which is made impossible by the repulsion of the electrons in the double bond or aromatic ring.



no S_N1, no S_N2

a vinyl halide
(烯基卤化物)

an aryl halide
(芳基卤化物)

7-12B Leaving-Group Effects

The leaving group is breaking its bond to carbon in the rate-limiting ionization step of the S_N1 mechanism. A highly polarizable leaving group helps stabilize the rate-limiting transition state through partial bonding as it leaves. The leaving group should be a weak base, very stable after it leaves with the pair of electrons that bonded it to carbon.

Figure 7-7 shows the transition state of the ionization step of the S_N1 reaction. Notice how the leaving group is taking on a negative charge while it stabilizes the new carbocation through partial bonding. The leaving group should be stable as it takes on this negative charge, and it should be polarizable to engage in effective partial bonding as it leaves. A good leaving group is just as necessary in the S_N1 reaction as it is in the S_N2, and similar leaving groups are effective for either reaction. Table 7-4 lists some common leaving groups.

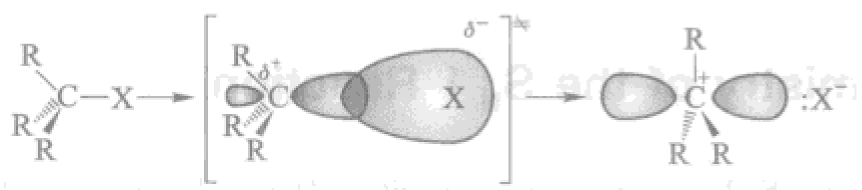


Figure 7-7 In the transition state of the S_N1 ionization, the leaving group is taking on a negative charge. The C—X bond is breaking, and a polarizable leaving group can still maintain substantial overlap.

PROBLEM 7-14

3-Bromocyclohexene is a secondary halide, and benzyl bromide is a primary halide. Both halides undergo S_N1 substitution about as fast as most tertiary halides. Use resonance structures to explain this enhanced reactivity.

3-bromocyclohexene benzyl bromide (苄基溴)

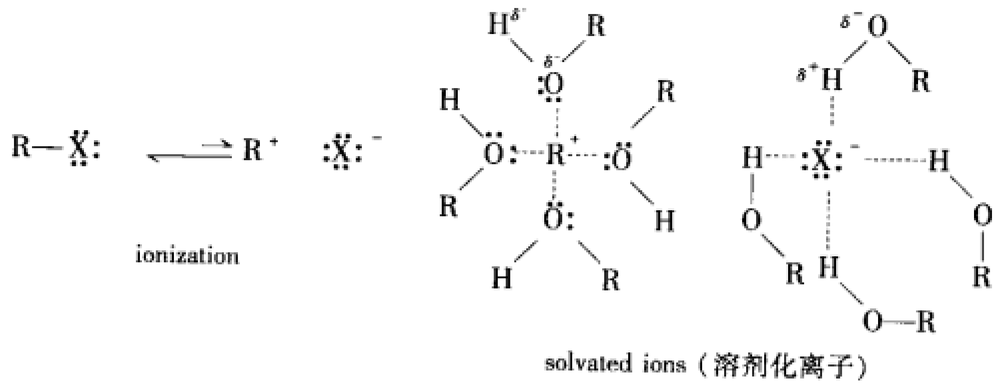
7-12C Solvent Effects

The S_N1 reaction goes much more readily in polar solvents that stabilize ions. The rate-limiting step forms two ions, and ionization is taking place in the transition state. Polar solvents solvate these ions by an interaction of the solvent's dipole moment with the charge of the ion. Protic solvents such as alcohols and water are even more effective solvents because anions form hydrogen bonds with the —OH hydrogen atom, and cations complex with the nonbonding electrons of the—OH oxygen atom.

TABLE 7-6 Dielectric Constants (ϵ) and Ionization Rates of *t*-Butyl Chloride in Common Solvents

Solvent	ϵ	Relative Rate	Solvent	ϵ	Relative Rate
water	78	8000	acetone	21	1
methanol	33	1000	diethyl ether	4.3	0.001
ethanol	24	200	hexane	2.0	<0.0001

Ionization of an alkyl halide requires formation and separation of positive and negative charges, similar to what happens when sodium chloride dissolves in water. Therefore, S_N1 reactions require highly polar solvents



that strongly solvate ions. One measure of a solvent's ability to solvate ions is its *dielectric constant* (ε), a measure of the solvent's polarity. Table 7-6 lists the dielectric constants of some common solvents and the relative ionization rates for *t*-butyl chloride in these solvents. Note that ionization occurs much faster in highly polar solvents such as water and alcohols. Although most alkyl halides are not soluble in water, they often dissolve in highly polar mixtures of acetone and alcohols with water.

7-13 Stereochemistry of the S_N1 Reaction

We saw (Section 7-11) that the S_N2 reaction is stereospecific: The nucleophile attacks from the back side of the electrophilic carbon atom, giving inversion of configuration. In contrast, the S_N1 reaction is not stereospecific. In the S_N1 mechanism, the carbocation intermediate is sp^2 hybridized and planar. A nucleophile can attack the carbocation from either face. Figure 7-8 shows the S_N1 solvolysis of a chiral compound, (*S*)-3-bromo-2,3-dimethylpentane, in ethanol. The carbocation is planar and achiral; attack from both faces gives both enantiomers of the product. Such a process, giving both enantiomers of the product (whether or not the two enantiomers are produced in equal amounts), is called **racemization**. The product is either racemic or at least less optically pure than the starting material.

If a nucleophile attacks the carbocation in Figure 7-8 from the front side (the side the leaving group left), the product molecule shows **retention of configuration.** Attack from the back side gives a product molecule showing **inversion of configuration.** Racemization is simply a combination of retention and inversion. When racemization occurs, the product is rarely completely racemic, however; there is often more inversion than reten-

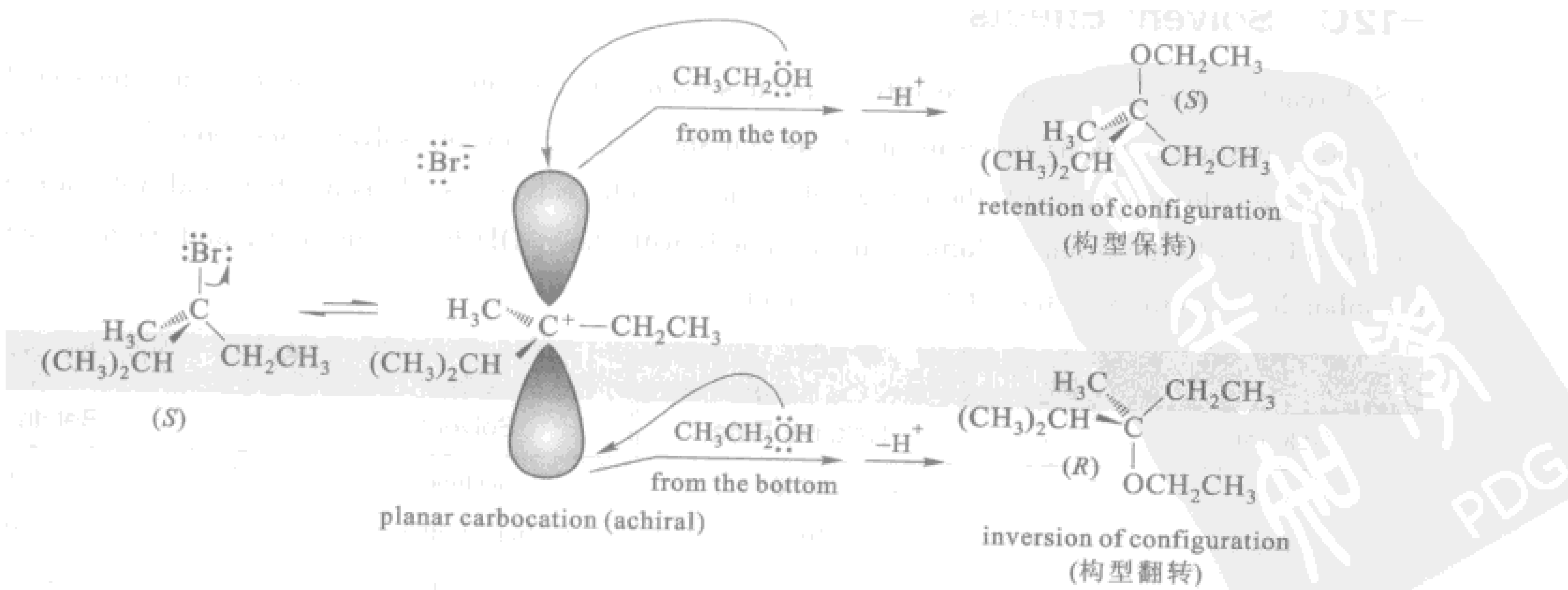


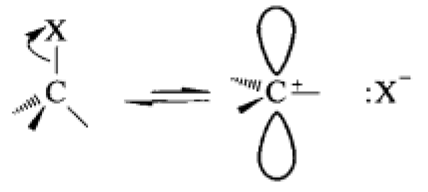
Figure 7-8 Racemization. An asymmetric carbon atom undergoes racemization when it ionizes to a planar, achiral carbocation. A nucleophile can attack the carbocation from either face, giving either enantiomer of the product.

tion of configuration. As the leaving group leaves, it partially blocks the front side of the carbocation. The back side is unhindered, so attack is more likely there.

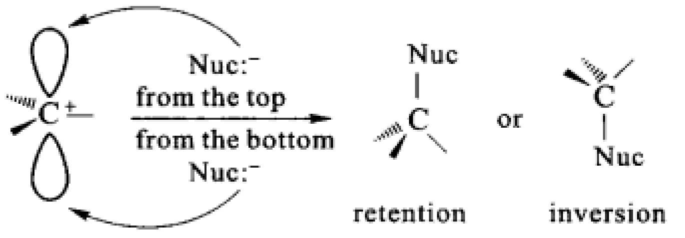
MECHANISM 7-4 Racemization in the S_N1 Reaction

The S_N1 reaction involves ionization to a flat carbocation, which can be attacked from either side.

Step 1: Ionization of a tetrahedral carbon gives a flat carbocation.



Step 2: A nucleophile may attack either side of the carbocation.



There two products may be different if the carbon atom is stereogenic.

Figure 7-9 shows a cyclic case where one of the faces of a cyclopentane ring has been "labeled" by a deuterium atom. Deuterium has the same size and shape as hydrogen and it undergoes the same reactions. It distinguishes between the two faces of the ring: The bromine atom is cis to the deuterium in the reactant, so the nucleophile is cis to the deuterium in the retention product. The nucleophile is trans to the deuterium in the inver-

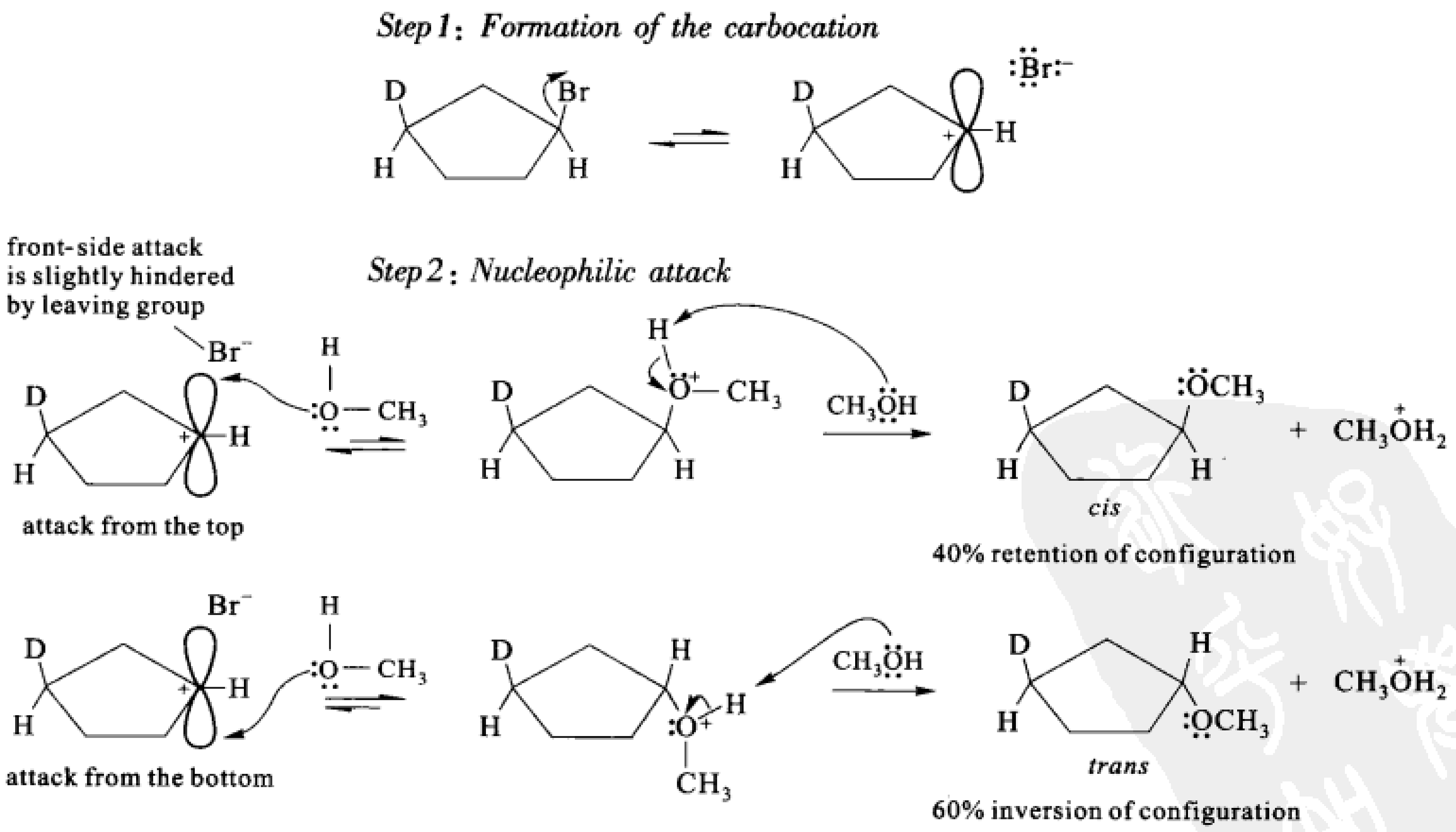


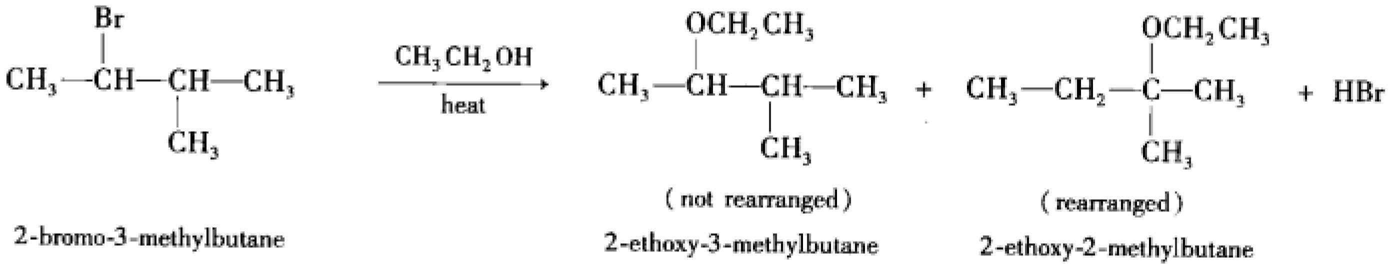
Figure 7-9 In the S_N1 reaction of *cis*-1-bromo-3-deuteriocyclopentane with methanol, the carbocation can be attacked from either face. Because the leaving group (bromide) partially blocks the front side as it leaves, back-side attack (inversion of configuration) is slightly favored.

sion product. The product mixture contains both cis and trans isomers, with the trans isomer slightly favored because the leaving group hinders approach of the nucleophilic solvent from the front side.

7-14 Rearrangements in S_N1 Reactions

Carbocations frequently undergo structural changes, called **rearrangements**, to form more stable ions. A rearrangement may occur after a carbocation has formed or it may occur as the leaving group is leaving. Rearrangements are not seen in S_N2 reactions, where no carbocation is formed and the one-step mechanism allows no opportunity for rearrangement.

An example of a reaction with rearrangement is the S_N1 reaction of 2-bromo-3-methylbutane in boiling ethanol. The product is a mixture of 2-ethoxy-3-methylbutane (not rearranged) and 2-ethoxy-2-methylbutane (rearranged).

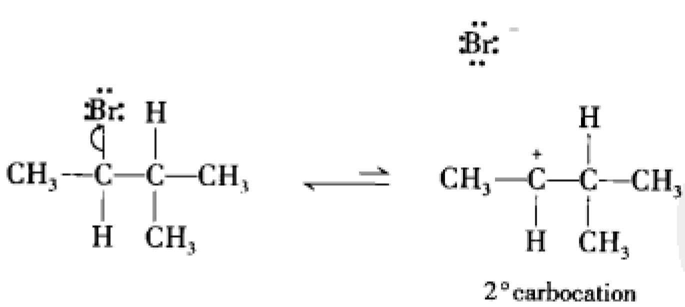


The rearranged product, 2-ethoxy-2-methylbutane, results from a **hydride shift**, the movement of a hydrogen atom with its bonding pair of electrons. A hydride shift is represented by the symbol ~ H. In this case, the hydride shift converts the initially formed secondary carbocation to a more stable tertiary carbocation. Attack by the solvent gives the rearranged product.

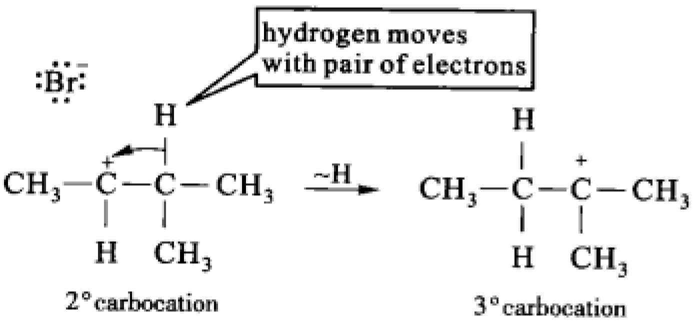
MECHANISM 7-5 Hydride Shift in an S_N1 Reaction

Carbocations often rearrange to form more stable carbocations. This may occur when a hydrogen atom moves with its bonding pair of electrons. Formally, this is the movement of a hydride ion ($H:^-$), although no actual free hydride ion is involved.

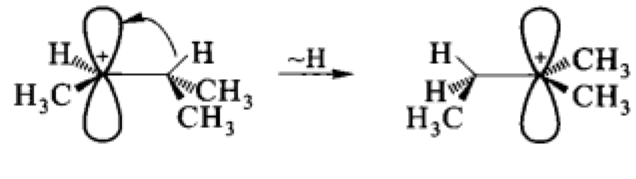
Step 1: Unimolecular ionization gives a carbocation.



Step 2: A hydride shift forms a more stable carbocation.

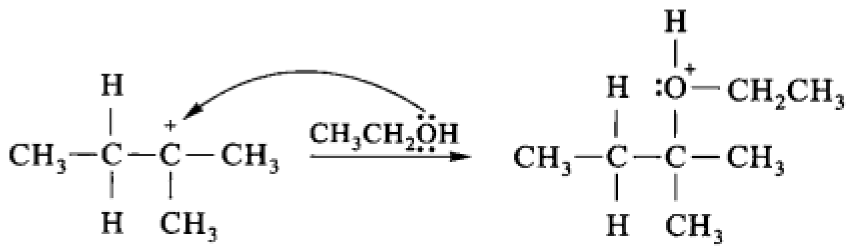


This rearrangement involves movement of a hydrogen atom with its bonding pair of electrons over to the empty *p* orbital of the carbocation. In three dimensions, the rearrangement looks like this:



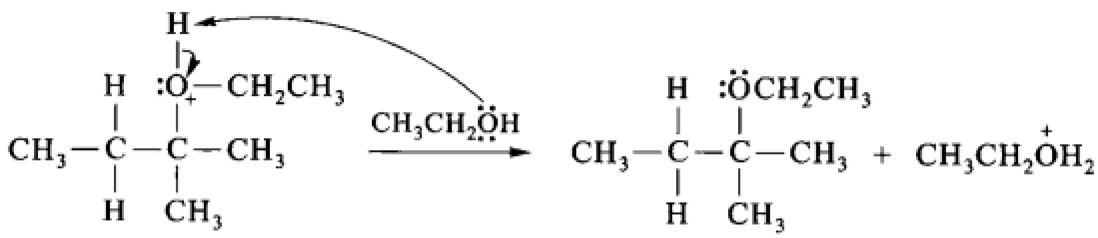
2° carbocation 3° carbocation

Step 3: Solvent (a weak nucleophile) attacks the rearranged carbocation.



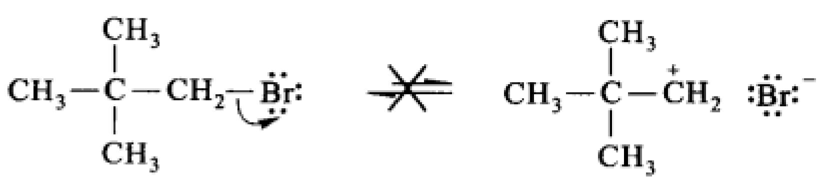
tertiary carbocation
(叔碳正离子)

Step 4: Deprotonation gives the rearranged product.



rearranged product(重排产物)

When neopentyl bromide is boiled in ethanol, it gives *only* a rearranged substitution product. This product results from a **methyl shift** (represented by the symbol $\sim CH_3$), the migration of a methyl group together with its pair of electrons. Without rearrangement, ionization of neopentyl bromide would give a very unstable primary carbocation.



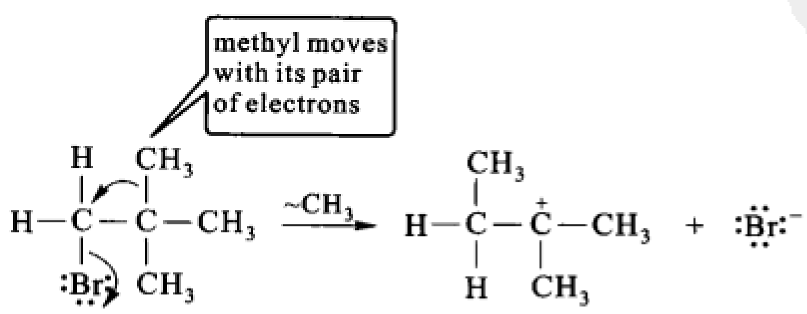
neopentyl bromide (新戊基溴) 1° carbocation

The methyl shift occurs *while* bromide ion is leaving, so that only the more stable tertiary carbocation is formed.

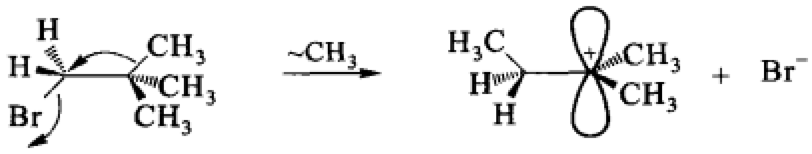
MECHANISM 7-6 Methyl Shift in an S_N1 Reaction

An alkyl group can rearrange to make a carbocation more stable.

Step 1: Ionization occurs with a methyl shift.

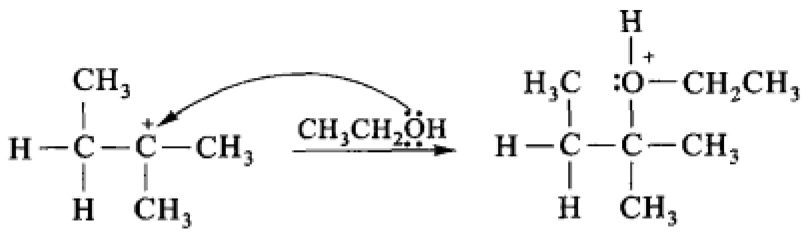


In three dimensions,



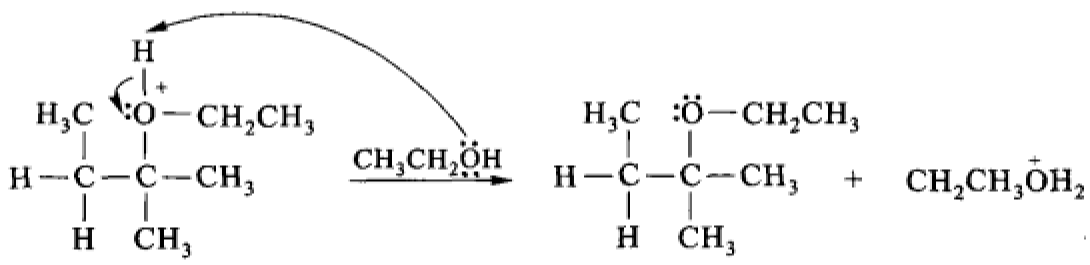
3° carbocation

Step 2: Attack by ethanol gives a protonated version of the rearranged product.



protonated product (质子化产物)

Step 3: Deprotonation gives the rearranged product.



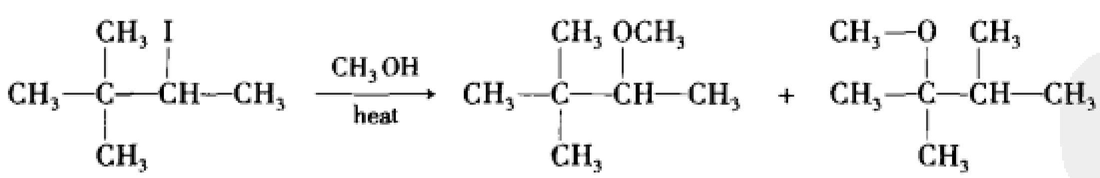
rearranged product

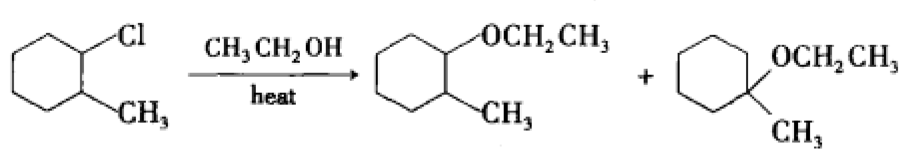
Because rearrangement is required for ionization, only rearranged products are observed.

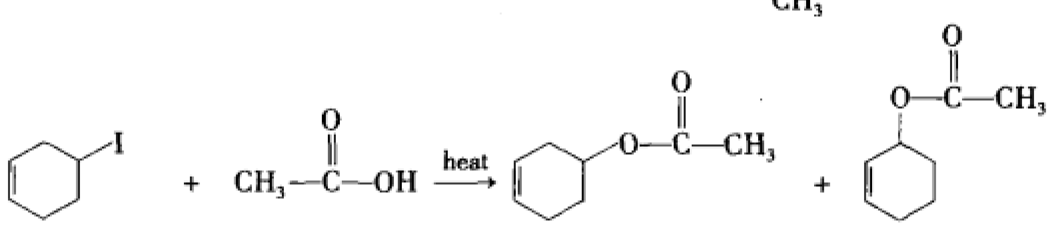
In general, we should expect rearrangements in reactions involving carbocations whenever a hydride shift or an alkyl shift can form a more stable carbocation. Most rearrangements convert 2° (or incipient 1°) carbocations to 3° or resonance-stabilized carbocations.

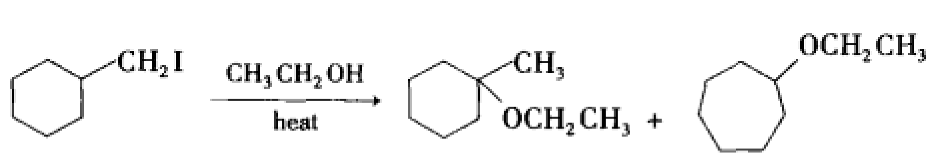
PROBLEM 7-15

Propose a mechanism involving a hydride shift or an alkyl shift for each solvolysis reaction. Explain how each rearrangement forms a more stable intermediate.

(a) 

(b) 

(c) 

(d) 

7–15 Comparison of S_N1 and S_N2 Reactions

Let's compare what we know about the S_N1 and S_N2 reactions, then organize this material into a brief table.

Effect of the Nucleophile The nucleophile takes part in the slow step (the only step) of the S_N2 reaction but not in the slow step of the S_N1. Therefore, a strong nucleophile promotes the S_N2 but not the S_N1. Weak nucleophiles fail to promote the S_N2 reaction; therefore, reactions with weak nucleophiles often go by the S_N1 mechanism if the substrate is secondary or tertiary.

S_N1: Nucleophile strength is unimportant (usually weak).

S_N2: Strong nucleophiles are required.

Effect of the Substrate The structure of the substrate (the alkyl halide) is an important factor in determining which of these substitution mechanisms might operate. Methyl halides and primary halides cannot easily ionize and undergo S_N1 substitution because methyl and primary carbocations are high in energy. They are relatively unhindered, however, so they make good S_N2 substrates.

Tertiary halides are too hindered to undergo S_N2 displacement, but they can ionize to form tertiary carbocations. Tertiary halides undergo substitution exclusively through the S_N1 mechanism. Secondary halides can undergo substitution by either mechanism, depending on the conditions.

S_N1 substrates:	$3° > 2°$	($1°$ and CH_3X are unlikely)
S_N2 substrates:	$CH_3X > 1° > 2°$	($3°$ is not suitable)

If silver nitrate ($AgNO_3$) is added to an alkyl halide in a good ionizing solvent, it removes the halide ion to give a carbocation. This technique can force some unlikely ionizations, often giving interesting rearrangements (see Problem 7–18.)

Effect of the Solvent The slow step of the S_N1 reaction involves formation of two ions. Solvation of these ions is crucial to stabilizing them and lowering the activation energy for their formation. Very polar ionizing solvents such as water and alcohols are needed for the S_N1. The solvent may be heated to reflux (boiling) to provide the energy needed for ionization.

Less charge separation is generated in the transition state of the S_N2 reaction. Strong solvation may weaken the strength of the nucleophile because of the energy needed to strip off the solvent molecules. Thus, the S_N2 reaction often goes faster in less polar solvents if the nucleophile will dissolve. Polar aprotic solvents may enhance the strength of weak nucleophiles.

S_N1: Good ionizing solvent required.

S_N2: May go faster in a less polar solvent.

Kinetics The rate of the S_N1 reaction is proportional to the concentration of the alkyl halide but not the concentration of the nucleophile. It follows a first-order rate equation.

The rate of the S_N2 reaction is proportional to the concentrations of both the alkyl halide [R—X] and the nucleophile [Nuc:$^-$]. It follows a second-order rate equation.

$$S_N1 \text{ rate} = k_r[\text{R—X}]$$
$$S_N2 \text{ rate} = k_r[\text{R—X}][\text{Nuc:}^-]$$

Stereochemistry The S_N1 reaction involves a flat carbocation intermediate that can be attacked from either face. Therefore, the S_N1 usually gives a mixture of inversion and retention of configuration.

The S_N2 reaction takes place through a back-side attack, which inverts the stereochemistry of the carbon atom. Complete inversion of configuration is the result.

S_N1 stereochemistry: Mixture of retention and inversion; racemization.

S_N2 stereochemistry: Complete inversion.

Rearrangements The S_N1 reaction involves a carbocation intermediate. This intermediate can rearrange, usually by a hydride shift or an alkyl shift, to give a more stable carbocation.

The S_N2 reaction takes place in one step with no intermediates. No rearrangement is possible in the S_N2 reaction.

S_N1: Rearrangements are common.

S_N2: Rearrangements are impossible.

PROBLEM 7-16

For each reaction, give the expected substitution product, and predict whether the mechanism will be predominantly first order or second order.

(a) 2-chloro-2-methylbutane + CH_3COOH

(b) isobutyl bromide + sodium methoxide

(c) 1-iodo-1-methylcyclohexane + ethanol

(d) cyclohexyl bromide + methanol

(e) cyclohexyl bromide + sodium ethoxide

PROBLEM 7-17

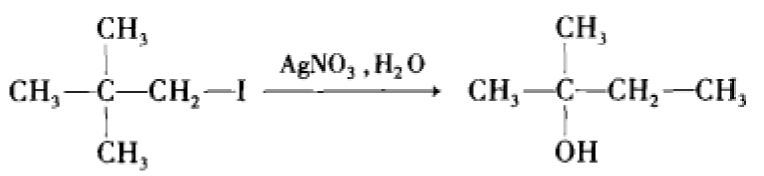
When (*R*)-2-bromobutane is heated with water, the S_N1 substitution proceeds twice as fast as the S_N2. Calculate the ee and the specific rotation expected for the product. The specific rotation of (*R*)-2-butanol is $-13.5°$.

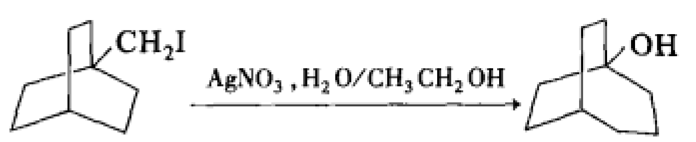
PROBLEM 7-18

A reluctant first-order substrate can be forced to ionize by adding some silver nitrate (one of the few soluble silver salts) to the reaction. Silver ion reacts with the halogen to form a silver halide (a highly exothermic reaction), generating the cation of the alkyl group.

$$R{-}X + Ag^+ \longrightarrow R^+ + AgX\downarrow$$

Give mechanisms for the following silver-promoted rearrangements.

(a) 

(b) 

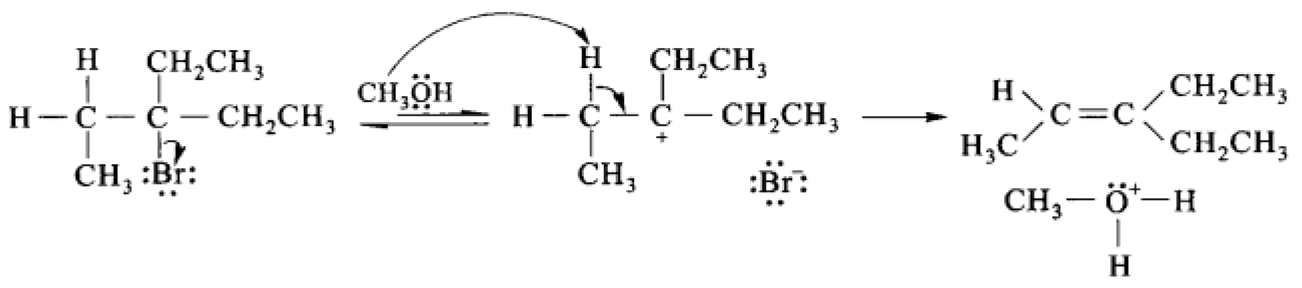
7-16 First-Order Elimination: The E1 Reaction

An **elimination** involves the loss of two atoms or groups from the substrate, usually with formation of a pi bond.

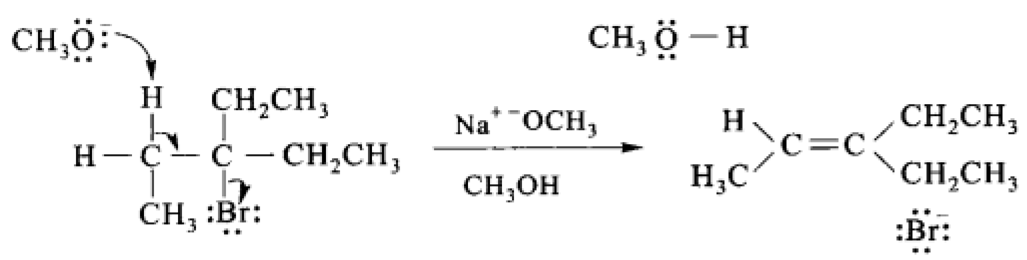
Elimination reactions frequently accompany and compete with substitutions. By varying the reagents and conditions, we can often modify a reaction to favor substitution or to favor elimination. First we will discuss eliminations by themselves. Then we consider substitutions and eliminations together, trying to predict what products and what mechanisms are likely with a given set of reactants and conditions.

Depending on the reagents and conditions involved, an elimination might be a first-order (E1) or second-order (E2) process. The following examples illustrate the types of eliminations we cover in this chapter.

E1



E2



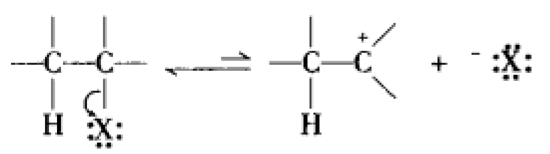
7-16A Mechanism and Kinetics of the E1 Reaction

The abbreviation **E1** stands for *Elimination*, *unimolecular.* The mechanism is called *unimolecular* because the rate-limiting transition state involves a single molecule rather than a collision between two molecules. The slow step of an E1 reaction is the same as in the S_N1 reaction: unimolecular ionization to form a carbocation. In a fast second step, a base abstracts a proton from the carbon atom adjacent to the C^+. The electrons that once formed the carbon-hydrogen bond now form a pi bond between two carbon atoms. The general mechanism for the E1 reaction is shown in the following Key Mechanism box.

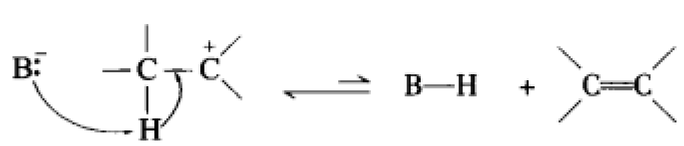
KEY MECHANISM 7-7 The E1 Reaction

The E1 reaction requires ionization to a carbocation intermediate like the S_N1, so it follows the same order of reactivity: $3° > 2° \gg 1°$ A base (usually weak) deprotonates the carbocation to give an alkene.

Step 1: Unimolecular ionization to give a carbocation (rate-limiting).

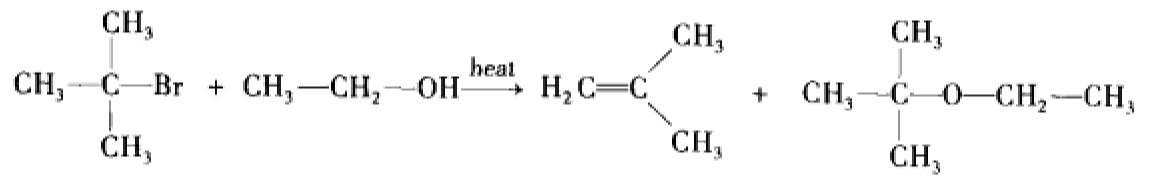


Step 2: Deprotonation by a weak base (often the solvent) gives the alkene (fast).



7-16B Competition with the S_N1 Reaction

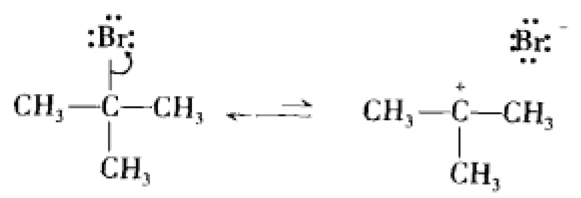
The E1 reaction almost always occurs together with the S_N1. Whenever a carbocation is formed, it can undergo either substitution or elimination, and mixtures of products often result. The following reaction shows the formation of both elimination and substitution products in the reaction of *t*-butyl bromide with boiling ethanol.



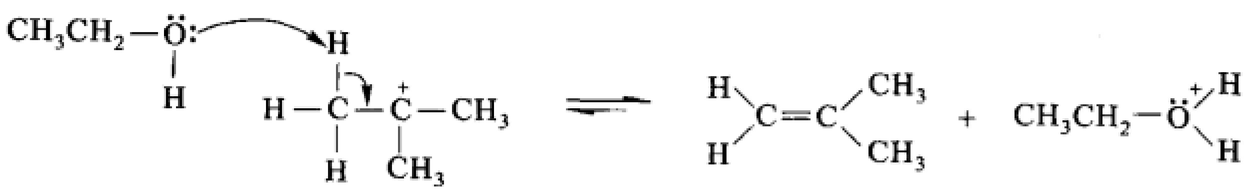
t-butyl bromide ethanol 2-methylpropene (E1 product) ethyl *t*-butyl ether (S_N1 product)

The 2-methylpropene product results from **dehydrohalogenation**, an elimination of hydrogen and a halogen atom. Under these first-order conditions (the absence of a strong base), dehydrohalogenation takes place by the E1 mechanism: Ionization of the alkyl halide gives a carbocation intermediate, which loses a proton to give the alkene. Substitution results from nucleophilic attack on the carbocation. Ethanol serves as a base in the elimination and as a nucleophile in the substitution.

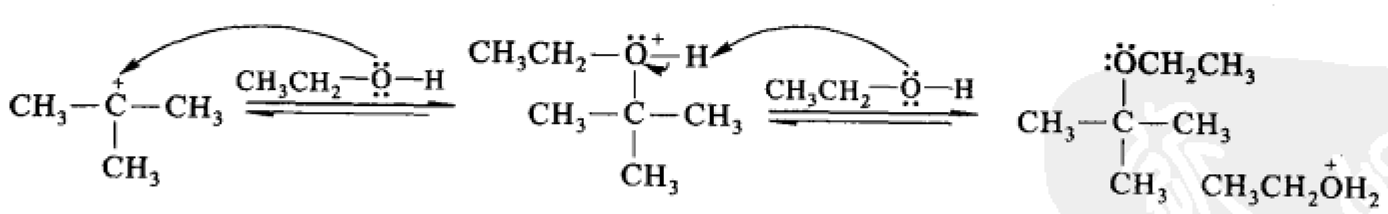
Step 1: Ionization to form a carbocation.



Step 2: (by the E1 mechanism): Basic attack by the solvent abstracts a proton to give an alkene.



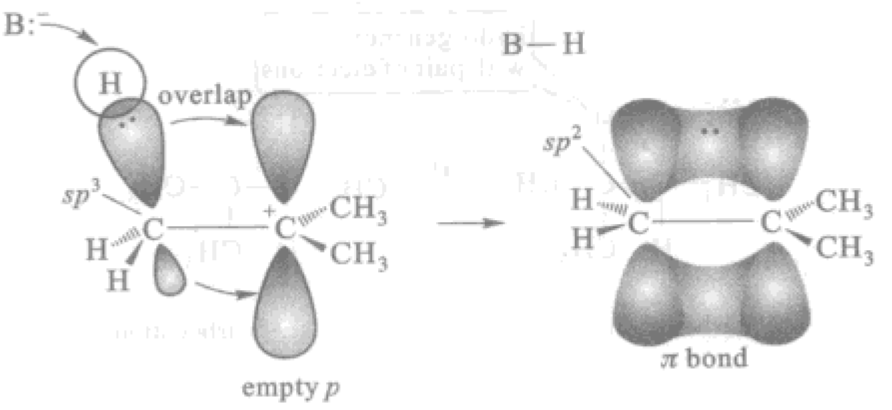
or, (by the S_N1 mechanism): Nucleophilic attack by the solvent on the carbocation.



Under ideal conditions, one of these first-order reactions provides a good yield of one product or the other. Often, however, carbocation intermediates react in two or more ways to give mixtures of products. For this reason, S_N1 and E1 reactions of alkyl halides are not often used for organic synthesis. They have been studied in great detail to learn about the properties of carbocations, however.

7-16C Orbitals and Energetics

In the second step of the E1 mechanism, the carbon atom next to the C^+ must rehybridize to sp^2 as the base attacks the proton and electrons flow into the new pi bond.



The potential-energy diagram for the E1 reaction (Figure 7-10) is similar to that for the S_N1 reaction. The ionization step is strongly endothermic, with a rate-limiting transition state. The second step is a fast exothermic deprotonation by a base. The base is not involved in the reaction until *after* the rate-limiting step so the rate depends only on the concentration of the alkyl halide. Weak bases are common in E1 reactions.

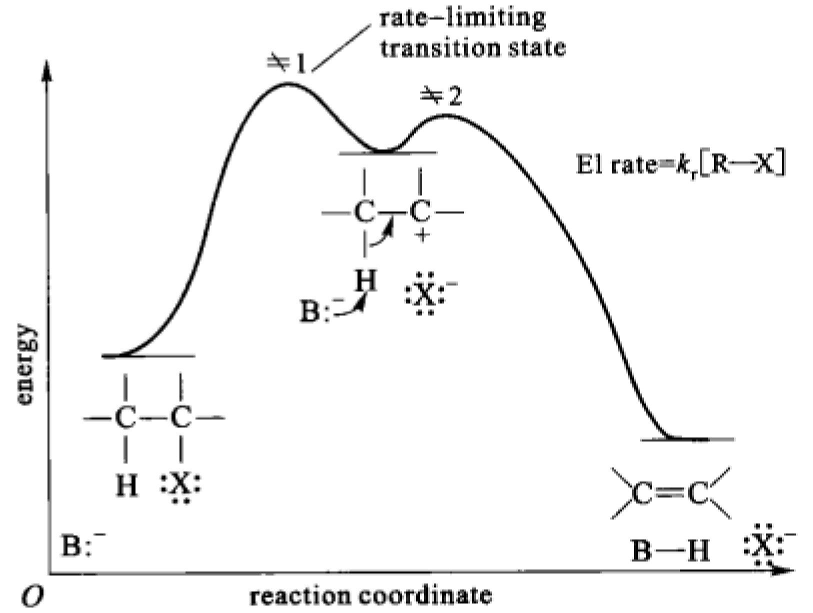


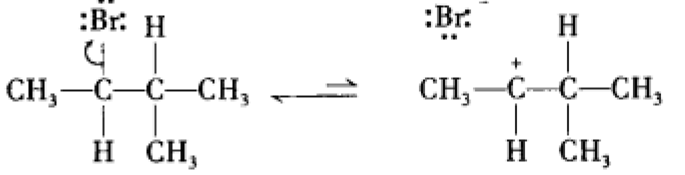
Figure 7-10 Reaction-energy diagram of the E1 reaction. The first step is a rate-limiting ionization. Compare this energy profile with that of the S_N1 reaction, Figure 7-6.

Like other carbocation reactions, the E1 may be accompanied by rearrangement. Compare the following E1 reaction (with rearrangement) with the S_N1 reaction of the same substrate, shown in Mechanism 7-5. Note that the solvent acts as a *base* in the E1 reaction and a *nucleophile* in the S_N1 reaction.

MECHANISM 7-8 Rearrangement in an E1 Reaction

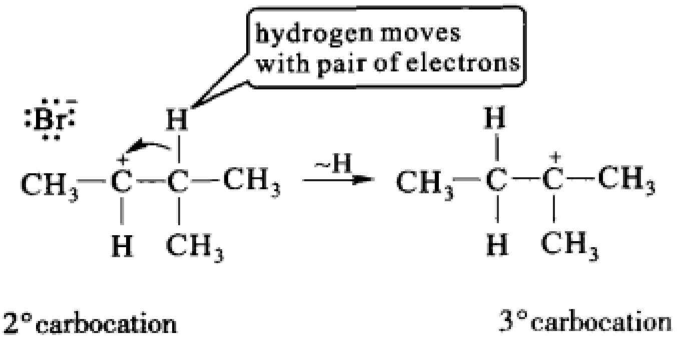
Like other reactions involving carbocations, the E1 may be accompanied by rearrangement.

***Step 1*:** Ionization to form a carbocation.

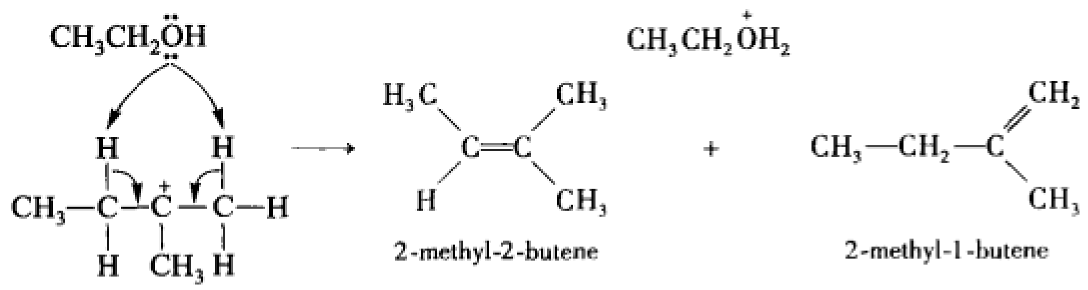


2-bromo-3-methylbutane   2° carbocation

***Step 2*:** A hydride shift forms a more stable carbocation.



***Step 3*:** The weakly basic solvent removes either adjacent proton.

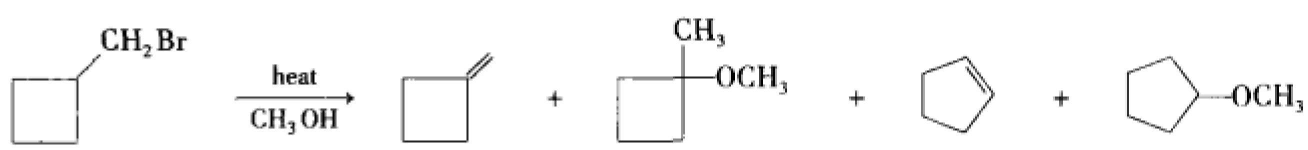


PROBLEM 7–19

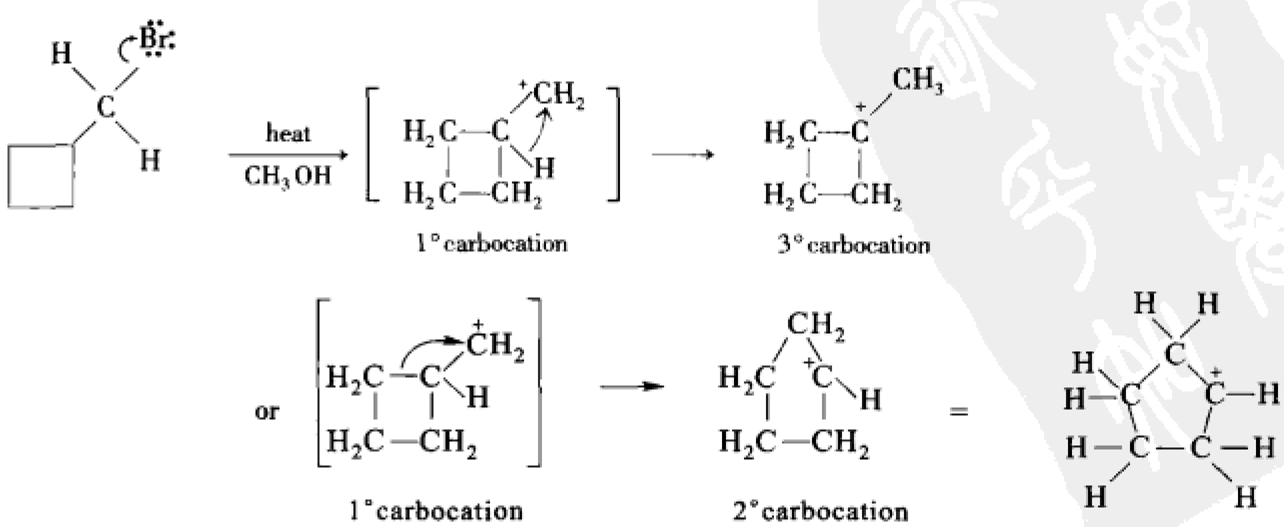
The solvolysis of 2-bromo-3-methylbutane potentially can give several products, including both E1 and S_N1 products from both the unrearranged carbocation and the rearranged carbocation. Mechanism Boxes 7–5 and 7–8 show the products from the rearranged carbocation. Summarize all the possible products, showing which carbocation they come from and whether they are the products of E1 or S_N1 reactions.

SOLVED PROBLEM 7–1 (PARTIALLY SOLVED)

When the following compound is heated in methanol, several different products are formed. Propose mechanisms to account for the four products shown.



Solution: With no strong base and a good ionizing solvent, we would expect a first-order reaction. But this is a primary alkyl helide, so ionization is difficult unless it rearranges. It might rearrange as it forms, but we'll imagine the cation forming then rearranging.



From these rearranged intermediates, either loss of a proton (E1) or attack by the solvent (S_N1) gives the observed products. Note that the actual reaction may give more than just these products, but the other products are not required for the problem.

PROBLEM 7−20

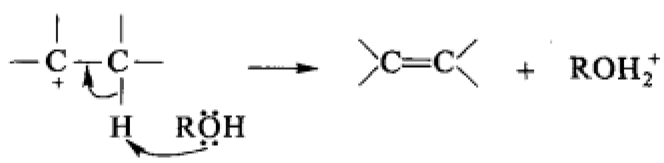
Finish Partially Solved Problem 7−1 by showing how the rearranged carbocations give the four products shown in the problem. Be careful when using curved arrows to show deprotonation and/or nucleophilic attack by the solvent. The curved arrows always show movement of electrons, not movement of protons or other species.

We can now summarize four ways that a carbocation can react to become more stable.

SUMMARY Carbocation Reactions

A carbocation can

1. React with its own leaving group to return to the reactant: $R^+ + :X^- \longrightarrow R{-}X$
2. React with a nucleophile to form a substitution product (S_N1): $R^+ + Nuc:^- \longrightarrow R{-}Nuc$
3. Lose a proton to form an elimination product (an alkene) (E1):



4. Rearrange to a more stable carbocation, then react further.

The order of stability of carbocations is: resonance-stabilized, 3° > 2° > 1°.

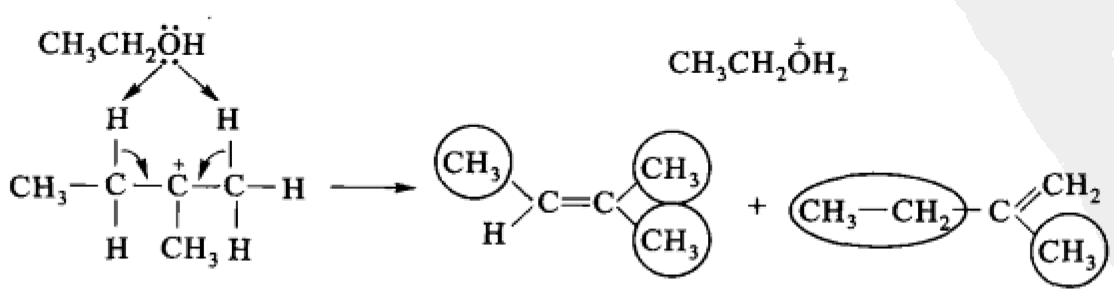
PROBLEM 7−21

Give the substitution and elimination products you would expect from the following reactions.

(a) 3-bromo-3-ethylpentane heated in methanol
(b) 1-iodo-1-methylcyclopentane heated in ethanol
(c) 3-bromo-2,2-dimethylbutane heated in ethanol
(d) iodocyclohexane + silver nitrate in water (see Problem 7−18)

7−17 Positional Orientation of Elimination: Zaitsev's Rule

Many compounds can eliminate in more than one way, to give mixtures of products. In many cases, we can predict which elimination product will predominate. In the example shown in Mechanism Box 7−8, the carbocation can lose a proton on either of two adjacent carbon atoms.



2-methyl-2-butene
trisubstituted, major (90%)

2-methyl-1-butene
disubstituted, minor (10%)

The first product has a *trisubstituted* double bond, with three substituents (circled) on the doubly bonded carbons. It has the general formula $R_2C{=}CHR$. The second product has a *disubstituted* double bond, with general formula $R_2C{=}CH_2$ (or $R{-}CH{=}CH{-}R$). In most E1 and E2 eliminations where there are two or more possible elimination products, *the product with the most substituted double bond will predominate.* This general principle is called **Zaitsev's rule**, and reactions that give the most substituted alkene are said to follow **Zaitsev orientation.**

ZAITSEV'S RULE: In elimination reactions, the most substituted alkene usually predominates.

$R_2C{=}CR_2$	>	$R_2C{=}CHR$	>	$RHC{=}CHR$ and $R_2C{=}CH_2$	>	$RHC{=}CH_2$
tetrasubstituted (四取代)		trisubstituted (三取代)		disubstituted (二取代)		monosubstituted (一取代)

This order of preference is the same as the order of stability of alkenes. We consider the stability of alkenes in more detail in Section 8−5, but for now, it is enough just to know that more substituted alkenes are more stable. In Chapter 8, we will study some unusual reactions where Zaitsev's rule does not apply.

PROBLEM 7−22

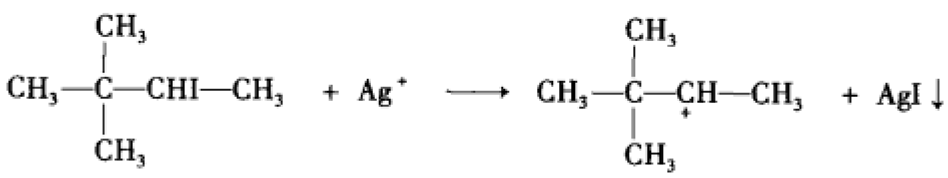
When 1-bromo-1-methylcyclohexane is heated in ethanol for an extended period of time, three products result: one ether and two alkenes. Predict the products of this reaction, and propose a mechanism for their formation. Predict which of the two alkenes is the major elimination product.

SOLVED PROBLEM 7−2

When 3-iodo-2,2-dimethylbutane is treated with silver nitrate in ethanol, three elimination products are formed. Give their structures, and predict which ones are formed in larger amounts.

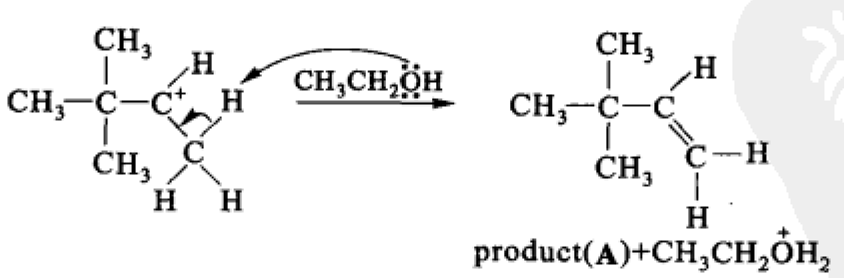
SOLUTION

Silver nitrate reacts with the alkyl iodide to give silver iodide and a cation.

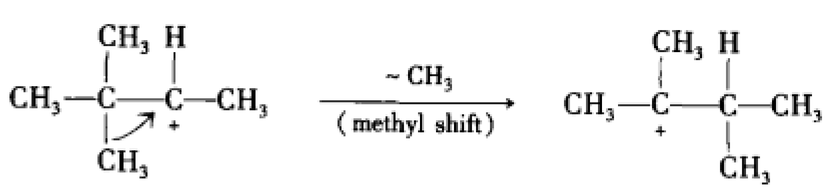


This secondary carbocation can lose a proton to give an unrearranged alkene (**A**), or it can rearrange to a more stable tertiary cation.

Loss of a proton



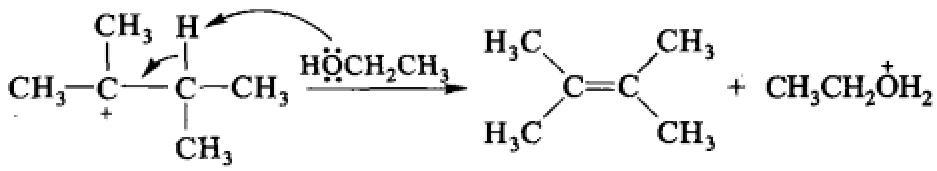
Rearrangement



2° carbocation 3° carbocation

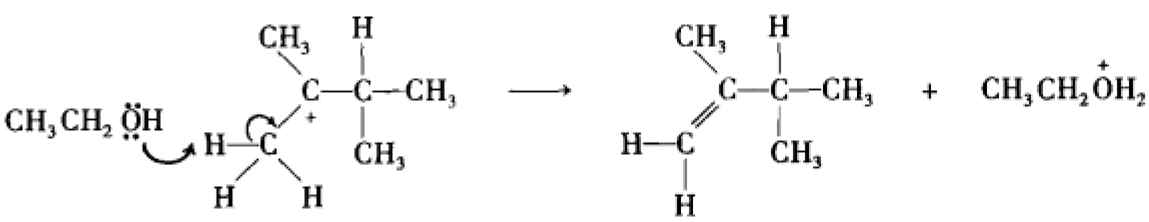
The tertiary cation can lose a proton in either of two positions. One of the products (**B**) is a tetrasubstituted alkene, and the other (**C**) is disubstituted.

Formation of a tetrasubstituted alkene



(B)
(tetrasubstituted)

Formation of a disubstituted alkene



(**C**)
(disubstituted)

Product **B** predominates over product **C** because the double bond in **B** is more substitued. Whether product **A** is a major product will depend on the specific reaction conditions and whether proton loss or rearrangement occurs faster.

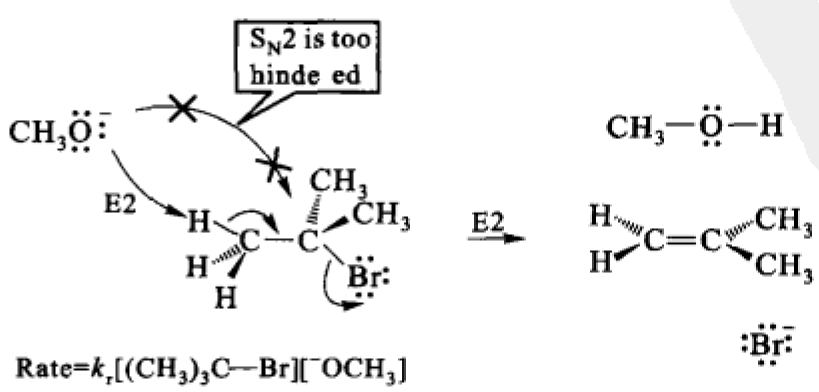
PROBLEM 7−23

Each of the two carbocations in Solved Problem 7−2 can also react with ethanol to give a substitution product. Give the structures of the two substitution products formed in this reaction.

7−18 Second-Order Elimination: The E2 Reaction

Eliminations can also take place under second-order conditions with a strong base present, As an example, consider the reaction of *t*-butyl bromide with methoxide ion in methanol.

This is a second-order reaction because methoxide ion is a strong base as well as a strong nucleophile. It attacks the alkyl halide faster than the halide can ionize to give a first -order reaction. No substitution product (methyl *t*-butyl ether) is observed, however. The S_N2 mechanism is blocked because the tertiary alkyl halide is too hindered. The observed product is 2-methylpropene, resulting from elimination of HBr and formation of a double bond.



$$\text{Rate}=k_r[(CH_3)_3C{-}Br][^-OCH_3]$$

The rate of this elimination is proportional to the concentrations of both the alkyl halide and the base, giving

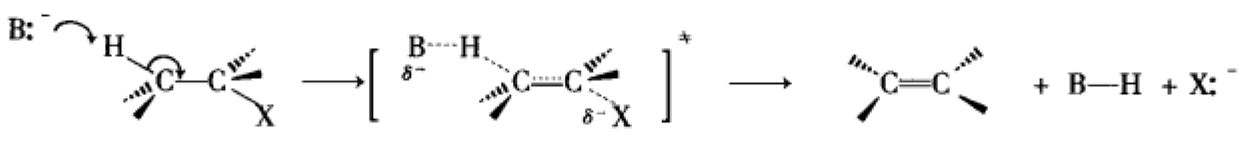
a second-order rate equation. This is a *bimolecular* process, with both the base and the alkyl halide participating in the transition state, so this mechanism is abbreviated **E2** for *Elimination*, *bimolecular*.

In the E2 reaction just shown, methoxide reacts as a *base* rather than as a *nucleophile*. Most strong nucleophiles are also strong bases, and elimination commonly results when a strong base/nucleophile is used with a poor S_N2 substrate such as a 3° or hindered 2° alkyl halide. Instead of attacking the back side of the hindered electrophilic carbon, methoxide abstracts a proton from one of the methyl groups. This reaction takes place in one step, with bromide leaving as the base is abstracting a proton.

In the general mechanism of the E2 reaction, a strong base abstracts a proton on a carbon atom adjacent to the one with the leaving group As the base abstracts a proton, a double bond forms and the leaving group leaves. Like the S_N2 reaction, the E2 is a *concerted* reaction in which bonds break and new bonds form at the same time, in a single step.

KEY MECHANISM 7-9 The E2 Reaction

The concerted E2 reaction takes place in a single step. A strong base abstracts a proton on a carbon next to the leaving group, and the leaving group leaves. The product is an alkene.



transition state

The order of reactivity for alkyl halides in E2 reactions is 3° > 2° > 1°.

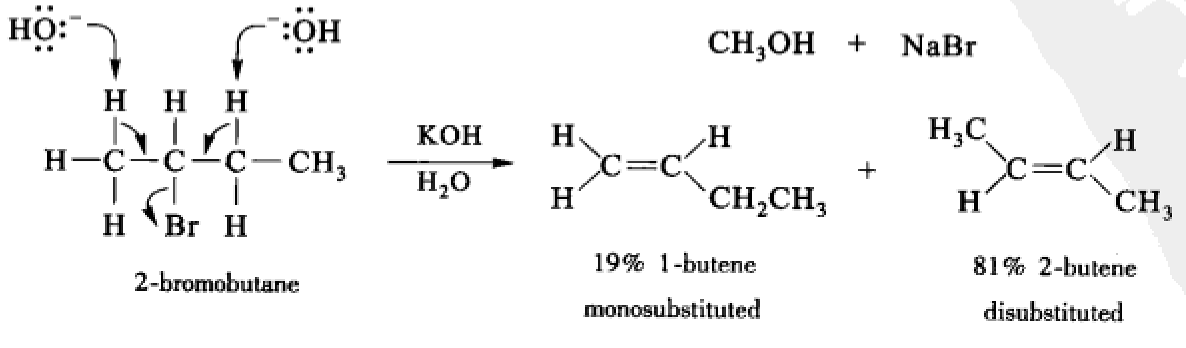
Under second-order conditions (strong base/nucleophile), S_N2 and E2 reactions may occur simultaneously and compete with each other.

Reactivity of the Substrate in the E2 The order of reactivity of alkyl halides toward E2 dehydrohalogenation is found to be

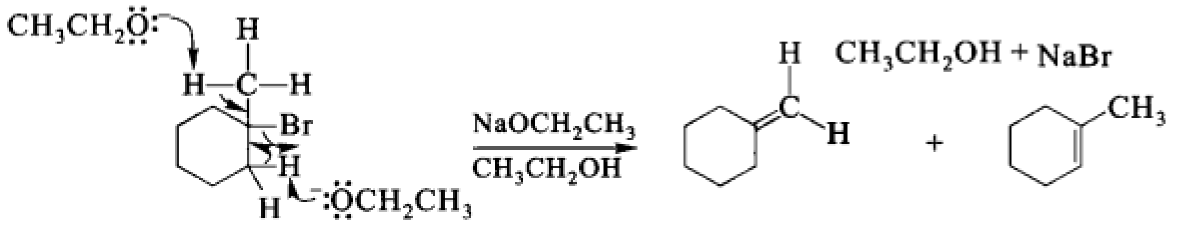
$$3° > 2° > 1°$$

This reactivity order reflects the greater stability of highly substituted double bonds. Elimination of a tertiary halide gives a more substituted alkene than elimination of a secondary halide, which gives a more substituted alkene than a primary halide. The stabilities of the alkene products are reflected in the transition states, giving lower activation energies and higher rates for elimination of alkyl halides that lead to highly substituted alkenes.

Mixtures of Products in the E2 The E2 reaction requires abstraction of a proton on a carbon atom next to the carbon bearing the halogen. If there are two or more possibilities, mixtures of products may result. In most cases, Zaitsev's rule predicts which of the possible products will be the major product: the most substituted alkene. For example, the E2 reaction of 2-bromobutane with potassium hydroxide gives a mixture of two products, 1-butene (a monosubstituted alkene) and 2-butene (a disubstituted alkene). As predicted by Zaitsev's rule, the disubstituted isomer 2-butene is the major product.



Similarly, the reaction of 1-bromo-1-methylcyclohexane with sodium ethoxide gives a mixture of a disubstituted alkene and a trisubstituted alkene. The trisubstituted alkene is the major product.



1-bromo-1-methylcyclohexane

methylenecyclohexane
disubstituted, minor

1-methylcyclohexene
trisubstituted, major

PROBLEM 7-24

1. Predict the elimination products of the following reactions. When two alkenes are possible, predict which one will be the major product. Explain your answers, showing the degree of substitution of each double bond in the products.
2. Which of these reactions are likely to produce both elimination and substitution products?

(a) 2-bromopentane + $NaOCH_3$

(b) 3-bromo-3-methylpentane + NaOMe (Me = methyl, CH_3)

(c) 2-bromo-3-ethylpentane + NaOH

(d) *cis*-1-bromo-2-methylcyclohexane + NaOEt (Et = ethyl, CH_2CH_3)

7-19 Stereochemistry of the E2 Reaction

Like the S_N2 reaction, the E2 follows a **concerted mechanism**: Bond breaking and bond formation take place at the same time, and the partial formation of new bonds lowers the energy of the transition state. Concerted mechanisms require specific geometric arrangements so that the orbitals of the bonds being broken can overlap with those being formed and the electrons can flow smoothly from one bond to another. The geometric arrangement required by the S_N2 reaction is a back-side attack; with the E2 reaction, a coplanar arrangement of orbitals is needed.

E2 elimination requires partial formation of a new pi bond, with its parallel *p* orbitals, in the transition state. The electrons that once formed a C—H bond must begin to overlap with the orbital that the leaving group is vacating. Formation of this new pi bond implies that these two sp^3 orbitals must be parallel so that pi overlap is possible as the hydrogen and halogen leave and the orbitals rehybridize to the *p* orbitals of the new pi bond.

Figure 7-11 shows two conformations that provide the necessary coplanar alignment of the leaving group, the departing hydrogen, and the two carbon atoms. When the hydrogen and the halogen are **anti** to each other ($\theta = 180°$), their orbitals are aligned. This is called the **anti-coplanar** conformation. When the hydrogen and the halogen eclipse each other ($\theta = 0°$), their orbitals are once again aligned. This is called the **syn-coplanar** conformation. Make a model corresponding to Figure 7-11, and use it to follow along with this discussion.

Of these possible conformations, the anti-coplanar arrangement is most commonly seen in E2 reactions. The transition state for the anti-coplanar arrangement is a staggered conformation, with the base far away from the leaving group. In most cases, this transition state is lower in energy than that for the syn-coplanar elimination.

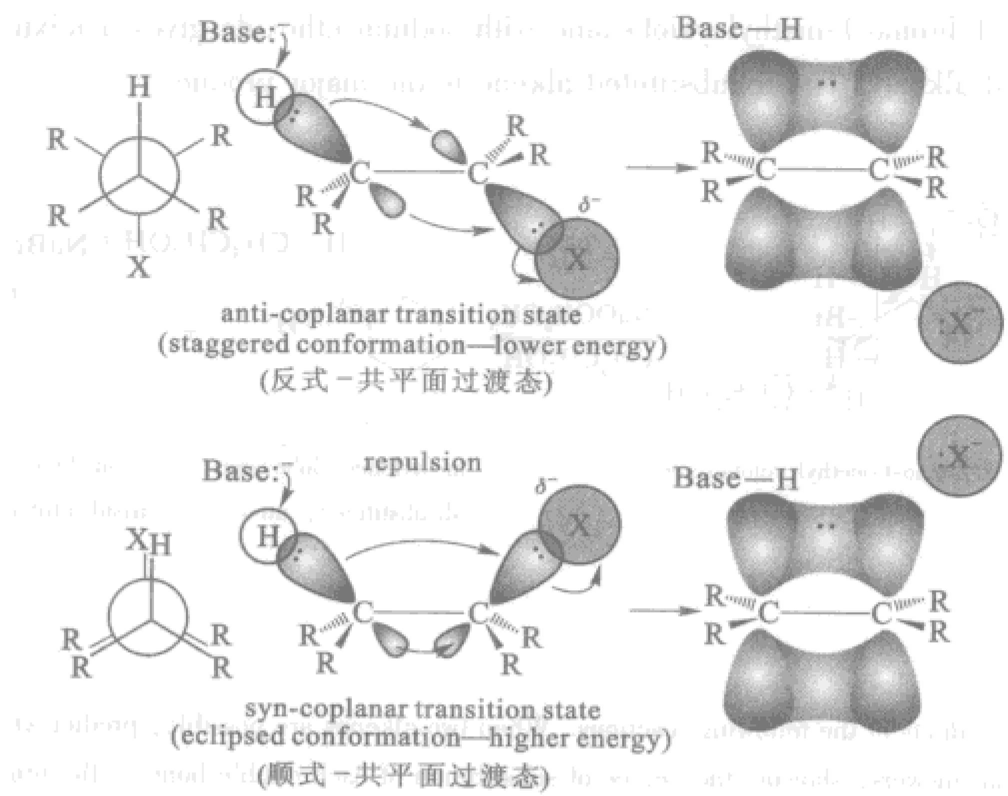
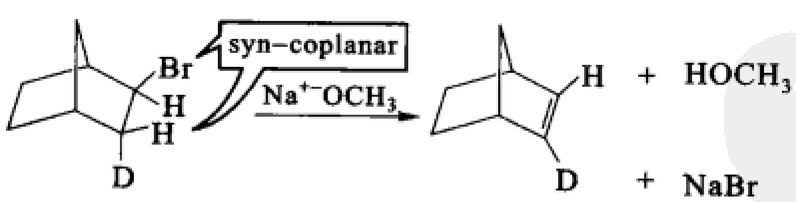


Figure 7-11 Concerted transition states of the E2 reaction. The orbitals of the hydrogen atom and the halide must be aligned so they can begin to form a pi bond in the transition state.

The transition state for syn-coplanar elimination is an eclipsed conformation. In addition to the higher energy resulting from eclipsing interactions, the transition state suffers from interference between the attacking base and the leaving group. To abstract the proton, the base must approach quite close to the leaving group. In most cases, the leaving group is bulky and negatively charged, and the repulsion between the base and the leaving group raises the energy of the syn-coplanar transition state.

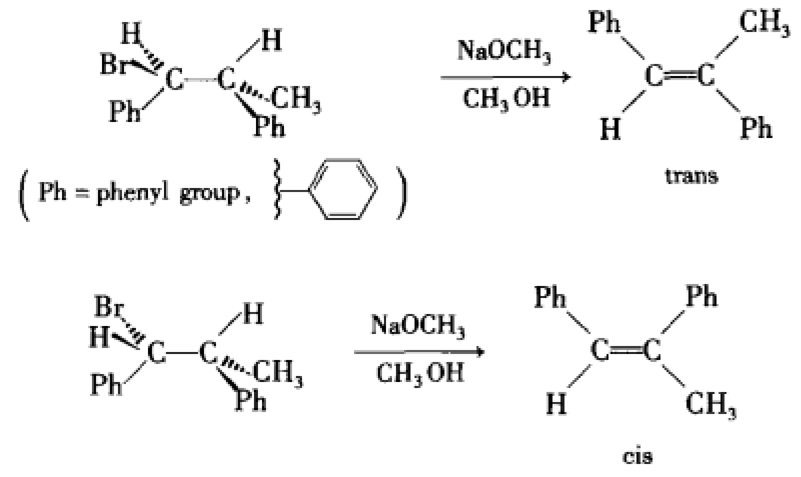
Some molecules are rigidly held in eclipsed (or nearly eclipsed) conformations, with a hydrogen atom and a leaving group in a syn-coplanar arrangement. Such compounds are likely to undergo E2 elimination by a concerted syn-coplanar mechanism. Deuterium labeling (using D, the hydrogen isotope with mass number 2) is used in the following reaction to show which atom is abstracted by the base. Only the hydrogen atom is abstracted, because it is held in a syn -coplanar position with the bromine atom. Remember that syn-coplanar eliminations are unusual, however; anti-coplanar eliminations are more common.



The E2 is a **stereospecific** reaction, because different stereoisomers of the starting material react to give different stereoisomers of the product. This stereospecificity results from the anti-coplanar transition state that is usually involved in the E2. We consider more of the implications of the anti-coplanar transition state in Chapter 8. For now, Problem 7-25 will give you an opportunity to build models and see how the stereochemistry of an E2 elimination converts different stereoisomers into different stereoisomers of the product.

PROBLEM 7-25

When the first compound shown here is treated with sodium methoxide, the only elimination product is the trans isomer. The second diastereomer gives only the cis product. Use your models and careful drawings of the transition states to explain these results.



7-20 Comparison of E1 and E2 Elimination Mechanisms

Let's summarize the major points to remember about the E1 and E2 reactions, focusing on the factors that help us predict which of these mechanisms will operate under a given set of experimental conditions. Then we will organize these factors into a short table.

Effect of the Base The nature of the base is the single most important factor in determining whether an elimination will go by the E1 or E2 mechanism. If a strong base is present, the rate of the bimolecular reaction will be greater than the rate of ionization, and the E2 reaction will predominate (perhaps accompanied by the S_N2).

If no strong base is present, with a good solvent a unimolecular ionization is likely, followed by loss of a proton to a weak base such as the solvent. Under these conditions, the E1 reaction usually predominates (always accompanied by the S_N1).

E1: Base strength is unimportant (usually weak).

E2: Strong bases are required.

Effect of the Solvent The slow step of the E1 reaction is the formation of two ions. Like the S_N1, the E1 reaction critically depends on polar ionizing solvents such as water and the alcohols.

In the E2 reaction, the transition state spreads out the negative charge of the base over the entire molecule. There is no more need for solvation in the E2 transition state than in the reactants. The E2 is therefore less sensitive to the solvent; in fact, some reagents are stronger bases in less polar solvents.

E1: Good ionizing solvent required.

E2: Solvent polarity is not so important.

Effect of the Substrate For both the E1 and the E2 reactions, the order of reactivity is

E1, E2: 3° > 2° > 1° (1° usually will not go E1)

In the E1 reaction, the rate-limiting step is formation of a carbocation, and the reactivity order reflects the stability of carbocations. In the E2 reaction, the more substituted halides generally form more substituted, more stable alkenes.

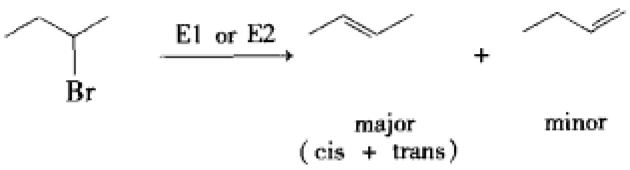
Kinetics The rate of the E1 reaction is proportional to the concentration of the alkyl halide [RX] but not to the concentration of the base. It follows a first-order rate equation.

The rate of the E2 reaction is proportional to the concentrations of both the alkyl halide [RX] and the base [B:⁻]. It follows a second-order rate equation.

E1 rate = k_r[RX]

E2 rate = k_r[RX][$B:^-$]

Orientation of Elimination In most E1 and E2 eliminations with two or more possible products, the product with the most substituted double bond (the most stable product) predominates. This principle is called **Zaitsev's rule**, and the most highly substituted product is called the **Zaitsev product.**



E1, E2: Usually Zaitsev orientation.

Stereochemistry The E1 reaction begins with an ionization to give a flat carbocation. No particular geometry is required.

The E2 reaction takes place through a concerted mechanism that requires a coplanar arrangement of the bonds to the atoms being eliminated. The transition state is usually anti-coplanar although it may be syn-coplanar in rigid systems.

E1: No particular geometry required for the slow step.

E2: Coplanar arrangement (usually anti) required for the transition state.

Rearrangements The E1 reaction involves a carbocation intermediate. This intermediate can rearrange, usually by the shift of a hydride or an alkyl group, to give a more stable carbocation.

The E2 reaction takes place in one step with no intermediates. No rearrangement is possible in the E2 reaction.

E1: Rearrangements are common.

E2: No rearrangements.

SOLVED PROBLEM 7-3

Predict the mechanisms and products of the following reactions.

(a)

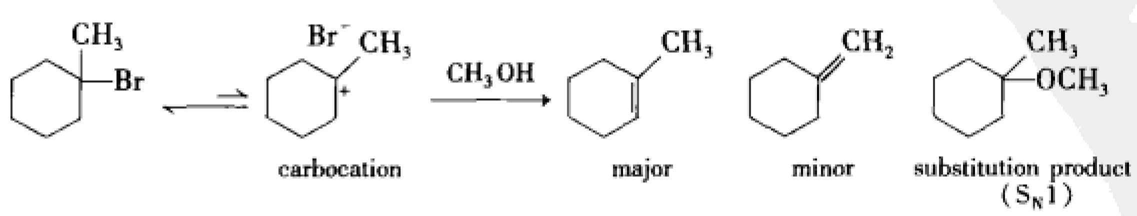
1-bromo-1-methylcyclohexane

(b) $CH_3-\underset{|}{\overset{Br}{CH}}-CH_2CH_2CH_2CH_3 \xrightarrow[CH_3OH]{NaOCH_3}$

2-bromohexane

SOLUTION

(a) There is no strong base or nucleophile present, so this reaction must be first order, with an ionization of the alkyl halide as the slow step. Deprotonation of the carbocation gives either of two elimination products, and nucleophilic attack gives a substitution product.



E1 elimination products

(b) This reaction takes place with a strong base, so it is second order. This secondary halide can undergo both S_N2 substitution and E2 elimination. Both products will be formed, with the relative proportions of substitution and elimination depending on the reaction conditions.

$$\underbrace{\underset{\text{major}}{CH_3{-}CH{=}CH{-}CH_2CH_2CH_3} \quad \underset{\text{minor}}{CH_2{=}CH{-}CH_2CH_2CH_2CH_3}}_{\text{E2 products}}$$

$$\underset{S_N2\text{ product}}{CH_3{-}\overset{\displaystyle OCH_3}{\overset{|}{C}H}{-}CH_2CH_2CH_2CH_3}$$

PROBLEM 7-26

Predict the products and mechanisms of the following reactions. When more than one product or mechanism is possible, explain which are most likely.

(a) 1-bromohexane + sodium ethoxide in ethanol

(b) 2-chlorohexane + $NaOCH_3$ in methanol

(c) *t*-butyl bromide + $NaOCH_2CH_3$ in ethanol

(d) *t*-butyl bromide heated in ethanol

(e) isobutyl iodide + KOH in ethanol/water

(f) isobutyl chloride + $AgNO_3$ in ethanol/water

(g) neopentyl bromide + $AgNO_3$ in ethanol/water

(h) 1-bromo-1-methylcyclopentane heated in methanol

(i) 1-bromo-1-methylcyclopentane + NaOEt in ethanol

Summary in Chinese

本 章 概 要

一、卤代烃的结构

根据卤代烃中卤原子所连接的碳原子的不同，卤代烃可分为卤代烷烃、卤代烯烃和卤代芳烃。卤代烷烃又可进一步分为伯、仲、叔卤代烷烃。在卤代烷烃中，由于卤原子的电负性大于 sp^3 杂化碳原子的电负性，所以碳卤键为极性键，成键电子偏向卤原子，直接与卤原子相连的碳原子带部分正电荷（δ^+），具有一定的亲电性，容易受到亲核试剂进攻发生化学反应；而卤原子带部分负电荷（δ^-），在反应中作为离去基团。在卤代烯烃和卤代芳烃中，卤原子与 sp^2 杂化碳原子成键，与卤代烷烃中的碳卤键相比，键的极性减小，使卤代烯烃和卤代芳烃中的碳卤键化学活性降低，不易发生亲核取代反应。

二、卤代烃的物理性质

由于卤代烃的分子极性、相对分子质量，以及分子表面积等因素的影响，卤代烃的沸点明显高于相应的烃类化合物的沸点。单卤代烷 RF 和 RCl 的相对密度小于 1，而 RBr 和 RI 的相对密度大于 1，多卤代烷和卤代芳烃的相对密度大于 1。

三、卤代烃的制备（preparation of alkyl halides，本章只介绍从烷烃出发，经过自由基卤代反应制备卤代烷）

1. 由烷烃制备卤代烷（from alkanes to alkyl halides，Sections 5-13 and 7-5）

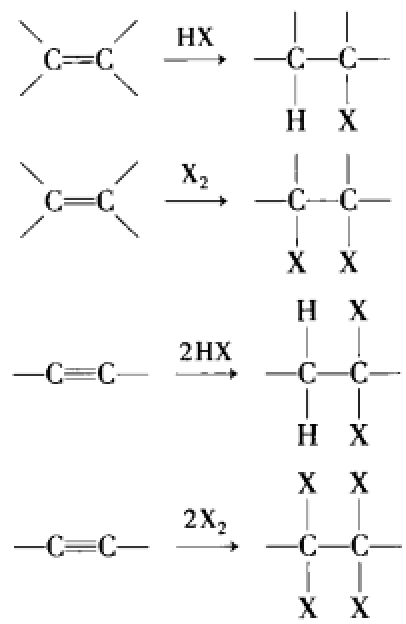
$$R{-}H \xrightarrow[\triangle \text{ or } h\nu]{X_2} R{-}X + H{-}X$$

☆ 烷烃的自由基氯代反应对不同氢原子的选择性较差，生成多种氯代物的混合物。因此，氯代反应用于合成时只能以某些特殊的烷烃为反应起始物，如环烷烃、新戊烷等分子中所有氢原子反应活性相同的烷烃，通过控制卤素的加入量，制备单卤代物。以含叔碳烷烃、烯丙型（allylic compounds）或苯甲型（benzylic compounds）化合物为起始物，进行溴代反应，一般采用 Br_2 或 *N*－溴代丁二酰亚胺（NBS）为溴化剂。反应经过稳定自由基，对叔氢（3° H）、烯丙基位氢（allylic H）和苄基位氢（benzylic H）具有高选择性，由此可制备叔丁基溴、烯丙基溴和苄基溴化物。以烯丙基化合物为反应物时，应考虑烯丙基位移所生成的溴代产物。

$$RCH{=}CH{-}CH_3 + NBS \xrightarrow{h\nu} RCH{=}CH{-}CH_2Br + RCH(Br){-}CH{=}CH_2$$

以下两种用于制备卤代烷的反应将分别在第 9、10 和 15 章中介绍。

2. 由烯烃、炔烃制备卤代烷（from alkenes and alkynes to alkyl halides, Sections 9－3, 9－8 and 10－8）



3. 由醇制备卤代烷（from alcohols to alkyl halides, Sections 15－6, 15－7, 15－8）

$$R{-}OH \xrightarrow{HX,\ PX_3 \text{ or } SOCl_2} RX$$

四、卤代烃的化学性质

1. 卤代烃的亲核取代反应（nucleophilic substitution of alkyl halides）

(1) S_N2 亲核取代反应：

- 反应机理与动力学：协同反应机理（concerted mechanism），反应速率取决于卤代烷和亲核试剂（Nu^-）的浓度，为二级反应，又称双分子反应，$r = k_r[RX][Nu^-]$。
- 立体化学特征：在反应过程中，亲核试剂从离去基团背后进攻缺电子碳原子，导致碳原子构型翻转。当起始物为光活性卤代烷，并且与卤原子相连的碳原子为手性中心时，经过 S_N2 亲核取代反应后，手性碳原子的构型完全转化，得到与反应物构型相反的产物。因此，S_N2 反应是一种立体专一性反应（stereospecific reaction）。
- 过渡态与影响 S_N2 反应速率的关键因素：在 S_N2 亲核取代反应过渡态中，碳原子与亲核试剂间的新键部分生成，与卤素之间的旧键部分断裂，中心碳原子同时与 5 个原子或基团连接，空间上比较拥挤，使过渡态对于碳原子周围原子或基团的体积大小十分敏感。因此，卤代烷的空阻效应是影响 S_N2 反应的关键因素。
- 卤代烷的空阻和电子效应对 S_N2 反应速率的影响：与卤原子相连的碳原子上带体积小的原子或基

团可使过渡态的能量降低，从而提高 S_N2 反应速率，相反，碳原子上带体积较大的原子或基团可使反应速率明显降低。除空阻效应外，与卤原子相连的碳原子上的其他原子或基团的电子效应亦可影响卤代烷的 S_N2 反应速率。吸电子基团可使碳原子上的缺电子性增强，更容易被亲核进攻，使反应速率加快。相反，给电子基团使反应速率降低。综合考虑卤代烷的空阻和电子效应，不同卤代烷的 S_N2 反应速率相对顺序为：$RCOCH_2X \gg PhCH_2X > CH_2=CH_2CH_2X > CH_3X > 1° RX > 2° RX$。叔卤代烷的空阻太大，不能进行 S_N2 亲核取代反应。

(2) S_N1 亲核取代反应：

- 反应机理与动力学：碳正离子机理，反应速率只取决于卤代烷的浓度，与亲核试剂的浓度无关，为一级反应，又称单分子反应，$r = k_r[RX]$。
- 立体化学特征：由于在反应过程中生成 sp^2 杂化的碳正离子，未杂化的 p 轨道垂直于 sp^2 杂化轨道所在平面，亲核试剂从平面上方或下方接近这个 p 轨道的概率相同，得到等量的构型保持和构型转化的产物。因此，S_N1 反应没有立体选择性。当反应起始物为光活性卤代烷，并且与卤原子相连的碳原子为手性中心时，经过 S_N1 反应后，发生外消旋化(racemization)，产物为外消旋体，无旋光活性。
- 中间体与影响 S_N1 反应速率的关键因素：在 S_N1 反应中，与后续步骤相比，第一步碳卤键断裂生成碳正离子为慢步骤，是 S_N1 反应的速率决定步骤。碳正离子的稳定性决定了第一步反应的速率，同时也决定了 S_N1 整个反应的速率。因此，卤代烷在卤离子解离后能否生成稳定的碳正离子是影响 S_N1 反应的关键因素。
- 共轭效应和电子效应对碳正离子稳定性的影响：如碳正离子上空的未杂化 p 轨道能够与相邻的 π 轨道或杂原子上带孤对电子的 p 轨道发生共轭作用，使正电荷离域，则可明显提高碳正离子的稳定性。此外，碳正离子上取代基的电子效应亦可影响碳正离子的稳定性。吸电子基团可使碳正离子上的电荷更强，从而降低碳正离子的稳定性；反之，给电子基团，包括 R 基团的超共轭效应可使碳正离子稳定性提高。综合考虑共轭效应和电子效应的影响，不同碳正离子的稳定性相对顺序为：$Ph_3C^+ > 3° C^+ > PhCH_2^+ > CH_2=CHCH_2^+ > 2° C^+$。$S_N1$ 反应速率的相对顺序与碳正离子稳定性顺序一致。在无强离子化试剂(如 $AgNO_3$)存在下，一般伯卤代烷不发生 S_N1 反应，只有特殊结构的伯卤代烷，如苄基、烯丙基、新戊基和异丁基卤代物等能发生 S_N1 亲核取代反应。
- 碳正离子重排：任何经过碳正离子中间体的反应，如果反应初始生成的碳正离子能够通过 1,2-氢转移或 1,2-烷基转移生成更稳定的碳正离子，那么反应给出的主产物一定是经过碳正离子重排后生成的产物。也就是说，碳正离子重排生成更稳定碳正离子的反应比其他后续反应快，总是优先发生。在碳正离子重排反应中，如果发生 1,2-烷基重排，则会使产物的分子骨架与反应物不同，因此，这种重排又称为分子骨架重排。由于伯碳正离子的不稳定性，在 S_N1 反应过程中，氢或烷基向伯碳转移并不经过伯碳正离子，而是氢或烷基向伯碳的转移与伯碳上卤离子离去同时发生，由此直接生成稳定碳正离子。对于一个经过碳正离子中间体的反应，在写反应产物时，必须考虑碳正离子是否会发生重排生成更稳定的碳正离子，然后由此出发生成最终产物。

(3) S_N1 与 S_N2 反应的影响因素和特征比较：

影响因素	S_N1 反应	S_N2 反应
反应物的影响[a]	S_N1 反应速率相对顺序： $3° RX > PhCH_2X >$ $R_2C=CHCH_2X > 2°RX$	S_N2 反应速率相对顺序： $RCOCH_2X \gg PhCH_2X >$ $R_2C=CHCH_2X > CH_3X > 1° RX > 2°RX$
亲核试剂的影响	改变亲核试剂浓度和强度对 S_N1 反应均无影响，使用弱亲核试剂或以溶剂(H_2O、ROH)作亲核试剂对 S_N1 反应有利	增加亲核试剂浓度和强度均可加快 S_N2 反应[b]

续表

影响因素	S_N1 反应	S_N2 反应
溶剂的影响	使用质子型溶剂(ROH、H_2O 等),增加溶剂极性可加速 S_N1 反应	非质子型极性溶剂有利于 S_N2 反应[c],如丙酮、二甲基甲酰胺(DMF)、冠醚等,亦可使用便宜的质子型溶剂
离去基团的影响	离去基团为弱碱时,对 S_N1 和 S_N2 反应都有利	
离子化试剂的影响	加 $AgNO_3$ 可促使难于生成稳定碳正离子的卤代烷离子化,有利于 S_N1 反应	
反应机理	两步反应(单分子、碳正离子机理)	一步反应(双分子、协同反应机理)
动力学	一级反应 $r=k_r[RX]$	二级反应 $r=k_r[RX][Nu^-]$
影响反应速率的关键因素	碳正离子稳定性	过渡态中心碳原子周围五个原子或基团的拥挤程度
RX 取代基的影响	与卤原子连接的碳原子上的取代基体积大小对 S_N1 反应无影响,吸电子取代基不利于 S_N1 反应	与卤原子连接的碳原子上的取代基体积增大不利于 S_N2 反应,吸电子取代基有利于 S_N2 反应
立体选择性	无立体选择性,可使手性卤代烷(RR′R″CX)外消旋化	立体专一性反应,手性卤代烷(RR′R″CX)构型完全转化
重排现象	普遍现象	不能发生

[a]烯基卤代物和芳基卤代物既不能发生 S_N1 反应,也不能发生 S_N2 反应。

[b]试剂的亲核性强弱主要取决于三个因素:试剂的碱性、极化度和体积。相同原子或同一周期原子作为亲核中心时,试剂的亲核性与碱性强弱顺序一致;同一族的原子作为亲核中心时,试剂的亲核性与原子极化度大小顺序一致,而与碱性强弱顺序相反;相同原子作为亲核中心时,试剂的亲核性与其体积大小顺序相反。此外,考虑试剂亲核性时,还应考虑溶剂效应。

[c]溶剂对 S_N2 反应的影响:如果亲核试剂带负电荷,生成过渡态时使负电荷分散到亲核试剂和离去基团上,体系极性减小,此时,增加溶剂极性不利于 S_N2 反应;如果带负电荷的亲核试剂能与质子溶剂发生溶剂化作用,减弱试剂亲核性也不利于 S_N2 反应;如果亲核试剂为中性分子(NH_3、RNH_2、PR_3 等),生成过渡态时体系极性增大,此时,增加溶剂极性有利于 S_N2 亲核取代反应。

2. 卤代烷烃的消除反应(elimination reactions of alkyl halides)

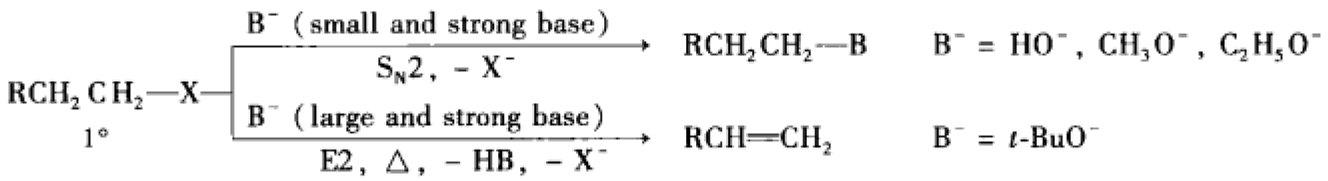
卤代烷烃消除 HX 的反应又称脱卤化氢反应(dehydrohalogenation),亦可分为双分子(E2)和单分子(E1)反应,下表给出 E1 和 E2 反应特征以及各种因素对 E1 和 E2 反应的影响。

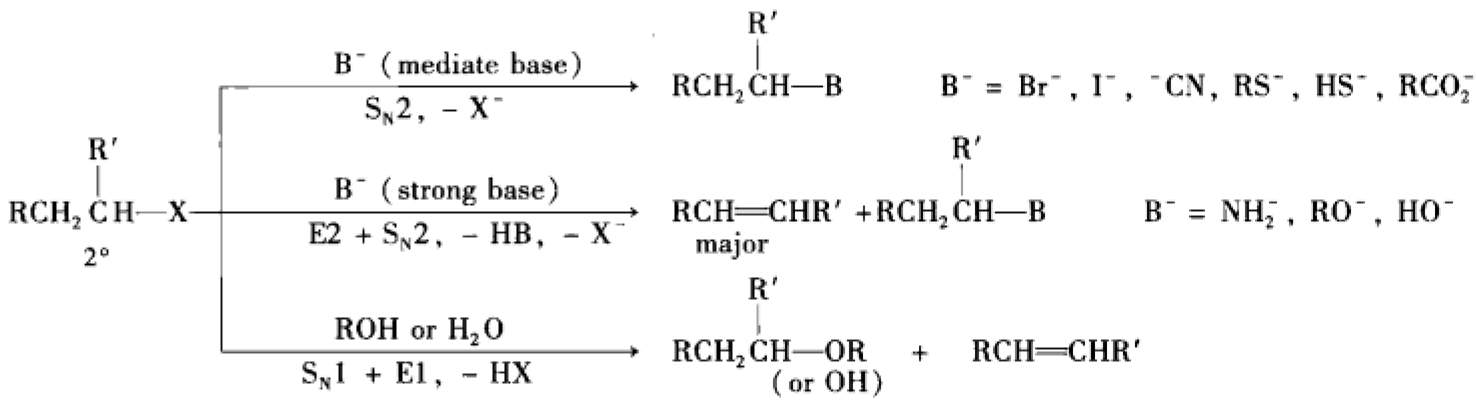
影响因素	E1 反应	E2 反应
反应物的影响	E1 反应速率相对顺序:3° RX > 2°RX	E2 反应速率相对顺序:3°RX > 2°RX > 1°RX
碱的影响	改变碱的浓度和强度对 E1 反应均无影响,使用弱碱或以溶剂作为碱时,对 E1 反应有利	增加碱的浓度和强度有利于 E2 反应
溶剂的影响	使用质子型溶剂、增加溶剂极性有利于 E1 反应	较低极性的溶剂(ROH)对 E2 反应有利
离去基团的影响	好的离去基团(弱碱)对 E1 和 E2 反应都有利	
反应机理	两步反应(单分子、碳正离子机理)	一步反应(双分子、协同反应机理)
动力学	一级反应,$r=k_r[RX]$	二级反应,$r=k_r[RX][B^-]$
区域选择性	符合札依采夫(Zaitsev)规则,取代基最多的烯烃为主产物,如能生成共轭烯烃,则共轭烯烃为主产物	一般情况下,符合札依采夫规则,但当卤代烷与体积大的碱反应时,取代基最少的烯烃为主产物,常为端位烯烃,符合霍夫曼(Hofmann)规则
立体选择性	无立体选择性,一般稳定性较好的反式烯烃的生成量比相应的顺式烯烃多	在 E2 反应过渡态中,β-H 与卤原子反式共平面,导致氢和卤原子反式消除,反应具有立体选择性
重排现象	普遍现象	不能发生

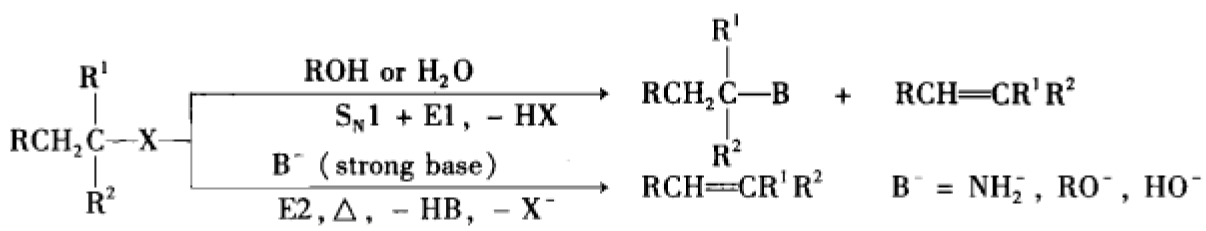
3. 取代与消除反应竞争基本规律小结

在卤代烷的反应中,取代与消除反应总是相互竞争的。一种卤代烷发生 S_N1 和 E1 反应的第一步,即速率决定步骤是完全相同的,生成相同的碳正离子中间体,因而,这两种反应总是不可避免地同时发生。降低反应温度可使 S_N1 取代反应产物为主产物。由于卤代烷脱卤化氢 E1 反应总是同时生成烯烃和取代产物的混合物,在烯烃合成上很少使用。在碱性条件下,E2 与 S_N2 反应互为竞争反应,碱既可进攻与卤原子相连的 α-碳原子,发生 S_N2 亲核取代反应,亦可进攻卤代烷中的 β-氢原子,发生 E2 消除反应。增加碱的强度和体积、增加卤代烷 β-碳上的空阻、提高反应温度,都有利于 E2 反应。相反,使用体积小的亲核试剂或极化度高但碱性小的亲核试剂有利于 S_N2 反应。以下以不同卤代烷为例,给出取代与消除竞争反应的一般规律。

(1) $CH_3{-}X \xrightarrow[S_N2,\ -X^-]{B^-} CH_3{-}B$ 碱性:$B^- > X^-$

(2) 

(3) 

(4) 

五、取代和消除反应在合成上的应用

1. 合成醇 (alcohol formation):

$$\underset{1°}{RX} \xrightarrow[S_N2]{^-OH} ROH \quad \underset{2°}{RX} \xrightarrow[(2)\ KOH,\ H_2O]{(1)\ CH_3CO_2^-,\ S_N2} ROH \quad \underset{3°}{RX} \xrightarrow[S_N1]{H_2O} ROH$$

☆ 2°RX 与强碱可发生 E2 消除反应,因此,必须先与中等强度的碱 $CH_3CO_2^-$ 反应,生成酯之后再水解生成 2°ROH。

2. 合成醚(ether formation):

$$\underset{1°}{R{-}X} \xrightarrow[S_N2]{^-OR'} ROR'$$ (Williamson 醚合成法):

3. 合成硫醇和硫醚 (thiol and sulfide formation):

$$\underset{1°,\ 2°}{R{-}X} \xrightarrow[S_N2]{^-SH} R{-}SH$$

$$\underset{1°,\ 2°}{R{-}X} \xrightarrow[S_N2]{^-SR'} R{-}S{-}R'$$

4. 合成胺（amine formation）：

$$R{-}X \xrightarrow[S_N2,\ -NH_4X]{NH_3} RNH_2$$

☆ 有 R_2NH、R_3N 多烷基胺生成，NH_3 必须大量过量，才能抑制多烷基胺生成。

5. 合成腈（nitrile formation）：

$$\underset{1°,\ 2°}{R{-}X} \xrightarrow[S_N2]{^-CN} R{-}CN$$

6. 合成炔（alkyne formation）：

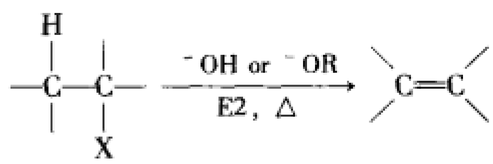
$$\underset{1°}{R{-}X} \xrightarrow[S_N2]{^-C{\equiv}CR'} R{-}C{\equiv}CR'$$

7. 合成氟或碘代烷（fluoroalkane and iodoalkane formation）：

$$R{-}X \xrightarrow[S_N2]{NaI} R{-}I \qquad R{-}Cl \xrightarrow[S_N2,\ CH_3CN]{KF,\ 18\text{-crown-}6} R{-}F$$

R—X ＝ 烯丙基或苄基卤代物

8. 合成烯烃（alkene formation）：



☆ 当 $^-OR = {}^-OCH_3$，$^-OC_2H_5$，$^-NH_2$ 等体积小的基团时，符合 Zaitsev（或 Saytseff）规则；当 ^-OR = t-BuO$^-$ 等体积大的基团时，符合 Hofmann 规则。

Essential Problem-Solving Skills in Chapter 7

1. Predict the products of S_N1, S_N2, E1, and E2 reactions, including stereochemistry.
2. Draw the mechanisms and energy profiles of S_N1, S_N2, E1, and E2 reactions.
3. Predict and explain the rearrangement of cations in first -order reactions.
4. Predict which substitutions or eliminations will be faster, based on differences in substrate, base/nucleophile, leaving group, or solvent.
5. Predict whether a reaction will be first -order or second-order.
6. When possible, predict predominance of substitution or elimination.
7. Use Zaitsev's rule to predict major and minor elimination products.

Study Problems

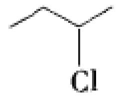
7-27 Define and give an example for each term.

(a) nucleophile(亲核试剂) (b) electrophile(亲电试剂) (c) leaving group(离去基团)
(d) substitution(取代) (e) S_N2 reaction (f) S_N1 reaction
(g) solvolysis(溶剂解) (h) elimination(消除) (i) E2 reaction
(j) E1 reaction (k) rearrangement(重排) (l) base
(m) steric hindrance(立体阻碍) (n) alkyl halide(卤代烷) (o) aryl halide(芳基卤代物)
(p) vinyl halide(乙烯基卤代物) (q) allylic halide(烯丙基卤代烷) (r) primary halide(伯卤代物)
(s) secondary halide(仲卤代物) (t) tertiary halide(叔卤代物) (u) anti elimination(反式消除)

(v) syn elimination(顺式消除)　　**(w)** stereospecific reaction(立体专一性反应)

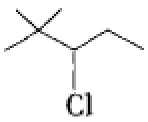
7-28 Predict the compound in each pair that will undergo the S_N2 reaction faster.

(a)

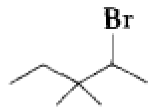
or 

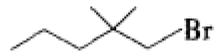
(b)

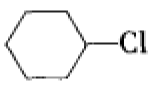
or

(c) 

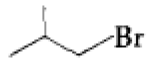
or

(d) 

or 

(e) 

or

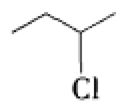
(f) 

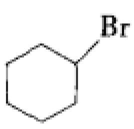
or

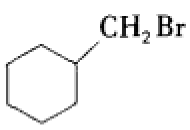
7-29 Predict the compound in each pair that will undergo solvolysis (in aqueous ethanol) more rapidly.

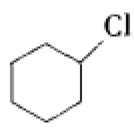
(a) $(CH_3CH_2)_2CH—Cl$ or $(CH_3)_3C—Cl$

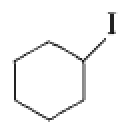
(b)

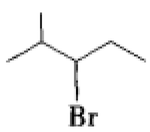
or 

(c) 

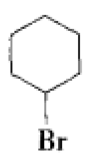
or 

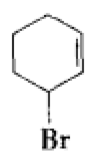
(d) 

or 

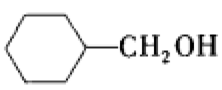
(e) 

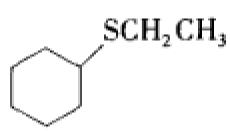
or

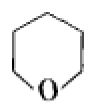
(f) 

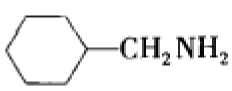
or 

7-30 Show how each compound might be synthesized by the S_N2 displacement of an alkyl halide.

(a) 

(b) 

(c) 

(d) 

(e) $H_2C═CH—CH_2CN$

(f) $(CH_3)_3C—OCH_3$

(g) $H—C≡C—CH_2CH_2CH_3$

7-31 **(a)** Give two syntheses for $(CH_3)_2CH—O—CH_2CH_3$, and explain which synthesis is better.

(b) A student wanted to synthesize methyl *t*-butyl ether, $CH_3—O—C(CH_3)_3$. He attempted the synthesis by adding sodium methoxide (CH_3ONa) to *t*-butyl chloride, but he obtained none of the desired product. Show what product is formed in this reaction, and give a better synthesis for methyl *t*-butyl ether.

7-32 When ethyl bromide is added to potassium *t*-butoxide, the product is ethyl *t*-butyl ether.

$$\underset{\text{ethyl bromide}}{CH_3CH_2—Br} + \underset{\text{potassium } t\text{-butoxide (叔丁醇钾)}}{(CH_3)_3C—O^-\,{}^+K} \longrightarrow \underset{\text{ethyl } t\text{-butyl ether}}{(CH_3)_3C—O—CH_2CH_3}$$

(a) What happens to the reaction rate if the concentration of ethyl bromide is doubled?

(b) What happens to the rate if the concentration of potassium *t*-butoxide is tripled and the concentration of ethyl bromide is doubled?

(c) What happens to the rate if the temperature is raised?

7-33 When *t*-butyl bromide is heated with ethanol, one of the products is ethyl *t*-butyl ether.

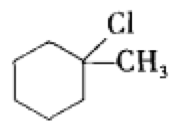
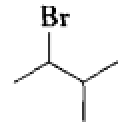
(a) What happens to the reaction rate if the concentration of ethanol is doubled?

(b) What happens to the rate if the concentration of *t*-butyl bromide is tripled and the concentration of ethanol is doubled?

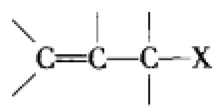
(c) What happens to the rate if the temperature is raised?

7-34 Chlorocyclohexane reacts with sodium cyanide (NaCN) in ethanol to give cyanocyclohexane. The rate of formation of cyanocyclohexane increases when a small amount of sodium iodide is added to the solution. Explain this acceleration in the rate.

7-35 Give the solvolysis products expected when each compound is heated in ethanol.

(a) (b)  (c)  (d)

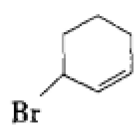
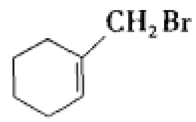
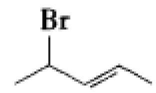
7-36 Allylic halides have the structure



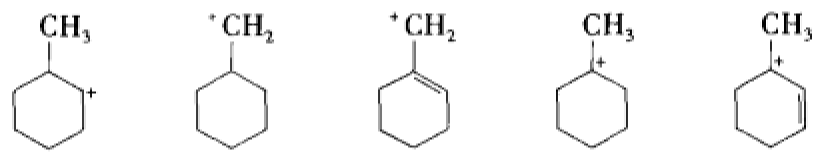
(a) Show how the first-order ionization of an allylic halide leads to a resonance-stabilized cation.

(b) Draw the resonance structures of the allylic cations formed by ionization of the following halides.

(c) Show the products expected from S_N1 solvolysis of these halides in ethanol.

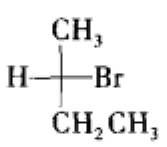
(i)  (ii)  (iii)  (iv)

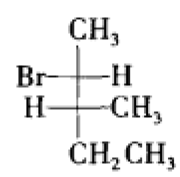
7-37 List the following carbocations in decreasing order of their stability.

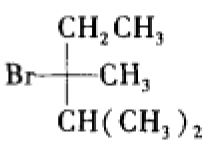


7-38 Two of the carbocations in Problem 7-37 are prone to rearrangement. Show how they might rearrange to more stable carbocations.

7-39 Draw perspective structures or Fischer projections for the substitution products of the following reactions.

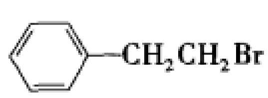
(a)  + NaCN $\xrightarrow{\text{acetone}}$

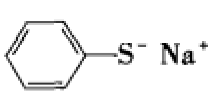
(b)  + NaOH $\xrightarrow{\text{water/acetone}}$

(c)  $\xrightarrow{\text{EtOH, heat}}$

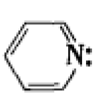
7-40 Predict the products of the following S_N2 reactions.

(a) $CH_3CH_2ONa + CH_3CH_2Cl \xrightarrow{\text{acetone}}$

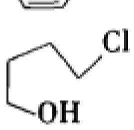
(b)  + NaCN $\xrightarrow{\text{acetone}}$

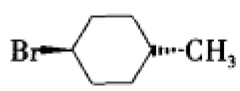
(c)  + $CH_3CH_2Br \longrightarrow$

(d) $CH_3(CH_2)_8CH_2Cl + Na^+ \ ^-:C{\equiv}CH \xrightarrow{\text{acetone}}$

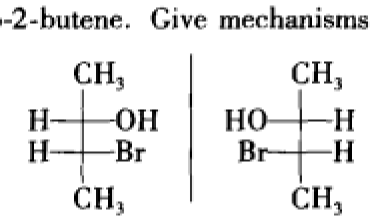
(e)  + $CH_3I \longrightarrow$

(f) $(CH_3)_3C—CH_2CH_2Br$ + excess $NH_3 \longrightarrow$

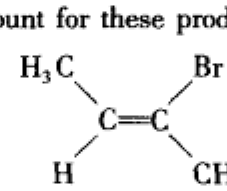
(g)  + NaOH $\longrightarrow$

(h)  $\xrightarrow[CH_3OH]{NaOH}$

7-41 When (±)-2,3-dibromobutane reacts with potassium hydroxide, some of the products are (2*S*,3*R*)-3-bromo-2-butanol and its enantiomer and *trans*-2-bromo-2-butene. Give mechanisms to account for these products.



(2*S*,3*R*) (2*R*,3*S*)
3-bromo-2-butanol



trans-2-bromo-2-butene

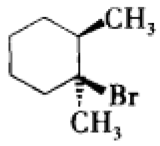
7-42 (a) Optically active 2-bromobutane undergoes racemization on treatment with a solution of KBr. Give a mechanism for this

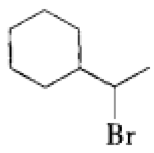
racemization.

(b) In contrast, optically active 2-butanol does not racemize on treatment with a solution of KOH. Explain why a reaction like that in part (a) does not occur.

(c) Optically active 2-butanol racemizes in dilute acid. Propose a mechanism for this racemization.

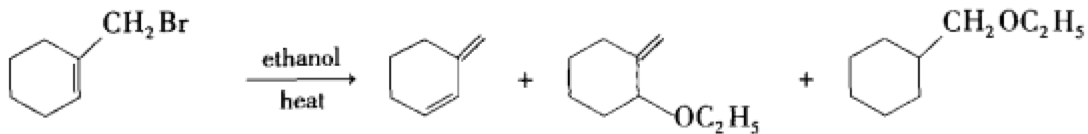
7−43 Predict the products of E1 elimination of the following compounds. Label the major products.

(a) 

(b) 

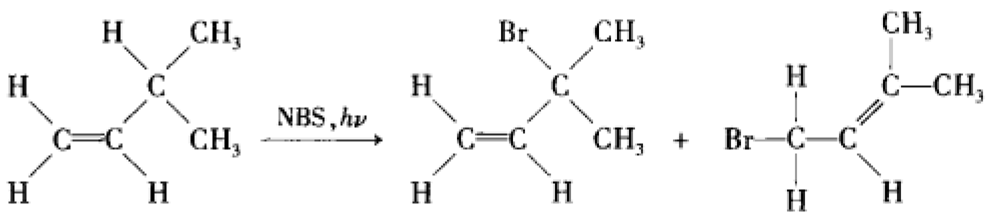
(c) $(CH_3)_3C-\underset{\displaystyle Br}{\underset{|}{CH}}-CH_3$

7−44 When 1-bromomethylcyclohexene undergoes solvolysis in ethanol, three major products are formed. Give mechanisms to account for these three products.



1-bromomethylcyclohexene

7−45 Give a mechanism to explain the two products formed in the following reaction.



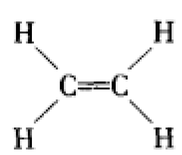
3-methyl-1-butene   not rearranged   rearranged

7−46 Because the S_N1 reaction goes through a flat carbocation, we might expect an optically active starting material to give a completely racemized product. In most cases, however, S_N1 reactions actually give more of the *inversion* product. In general, as the stability of the carbocation increases, the excess inversion product decreases. Extremely stable carbocations give completely racemic products. Explain these observations.

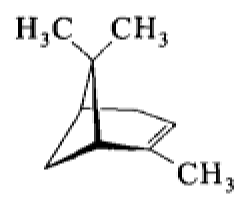
Chapter 8
Structure and Synthesis of Alkenes

8–1 Introduction

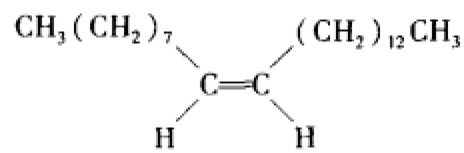
Alkenes are hydrocarbons with carbon-carbon double bonds. Alkenes are sometimes called **olefins**, a term derived from *olefiant gas*, meaning "oil-forming gas." This term originated with early experimentalists who noticed the oily appearance of alkene derivatives. Alkenes are among the most important industrial compounds, and many alkenes are also found in plants and animals. *Ethylene* is the largest-volume industrial organic compound, used to make polyethylene and a variety of other industrial and consumer chemicals. *Pinene* is a major component of *turpentine*, the paint solvent distilled from extracts of evergreen trees. *Muscalure* (*cis*-9-tricosene) is the sex attractant of the common housefly.



ethylene (ethene)
(乙烯)



α-pinene
(α-蒎烯)



cis-9-tricosene, "muscalure"
(二十三碳烯)(蚊蝇引诱剂)

The bond energy of a carbon-carbon double bond is about 611 kJ/mol, compared with the single-bond energy of about 347 kJ/mol. From these energies, we can calculate the approximate energy of a pi bond:

double-bond dissociation energy	611 kJ/mol
subtract sigma bond dissociation energy	(−) 347 kJ/mol
pi bond dissociation energy	264 kJ/mol

This value of 264 kJ/mol is much less than the sigma bond energy of 347 kJ/mol, showing that pi bonds should be more reactive than sigma bonds.

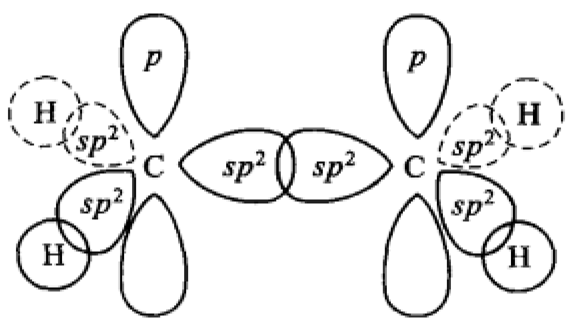
Because a carbon-carbon double bond is relatively reactive, it is considered to be a *functional group*, and its reactions are characteristic of alkenes. In previous chapters, we saw alkene synthesis by elimination reactions and we encountered a few reactions of alkenes. In this chapter, we study alkenes in more detail, concentrating on their properties and the ways they are synthesized.

8-2 The Orbital Description of the Alkene Double Bond

In a Lewis structure, the double bond of an alkene is represented by two pairs of electrons between the carbon atoms. The Pauli exclusion principle tells us that two pairs of electrons can go into one region of space between the carbon nuclei only if each pair has its own molecular orbital. Using ethylene as an example, let's consider how the electrons are distributed in the double bond.

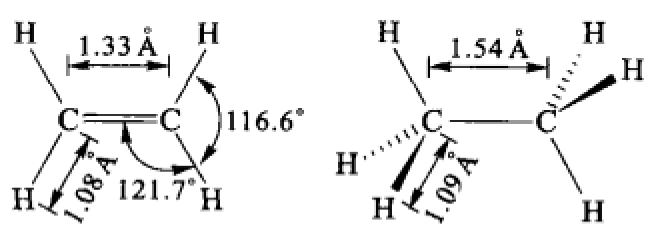
8-2A The Sigma Bond Framework

In Section 2-4, we saw how we can visualize the sigma bonds of organic molecules using hybrid atomic orbitals. In ethylene, each carbon atom is bonded to three other atoms (one carbon and two hydrogens), and there are no nonbonding electrons. Three hybrid orbitals are needed, implying sp^2 hybridization. We have seen (Section 2-4) that sp^2 hybridization corresponds to bond angles of about 120°, giving optimum separation of three atoms bonded to the carbon atom.



sigma bonding orbitals of ethylene

Each of the carbon-hydrogen sigma bonds is formed by overlap of an sp^2-hybrid orbital on carbon with the $1s$ orbital of a hydrogen atom. The C—H bond length in ethylene (1.08 Å) is slightly shorter than the C—H bond in ethane (1.09 Å) because the sp^2 orbital in ethylene has more s character (one-third s) than an sp^3 orbital (one-fourth s). The s orbital is closer to the nucleus than the p orbital, contributing to shorter bonds.



The remaining sp^2 orbitals overlap in the region between the carbon nuclei, providing a bonding orbital. The pair of electrons in this bonding orbital forms one of the bonds between the double-bonded carbon atoms. This bond is a sigma bond because its electron density is centered along the line joining the nuclei. The C=C bond in ethylene (1.33 Å) is much shorter than the C—C bond (1.54 Å) in ethane, partly because the sigma bond of ethylene is formed from sp^2 orbitals (with more s character) and partly because there are two bonds drawing the atoms together. The second carbon-carbon bond is a pi bond.

8-2B The Pi Bond

Two more electrons must go into the carbon-carbon bonding region to from the double bond in ethylene. Each carbon atom still has an unhybridized p orbital, and these overlap to form a pi-bonding molecular orbital. The two electrons in this orbital form the second bond between the double-bonded carbon atoms. For pi overlap to

occur, these p orbitals must be parallel, which requires that the two carbon atoms be oriented with all their C—H bonds in a single plane (Figure 8-1). Half of the pi-bonding orbital is above the C—C sigma bond, and the other half is below the sigma bond.

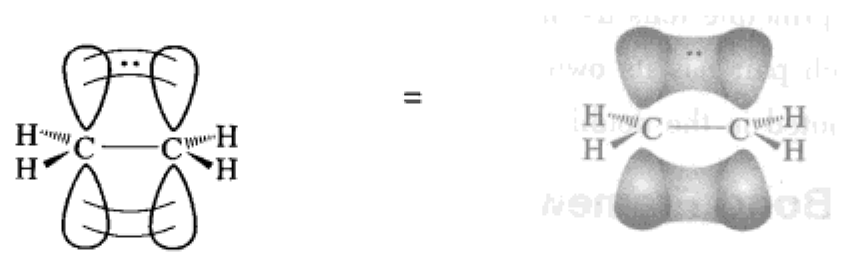


Figure 8-1 Parallel p orbitals in ethylene. The pi bond in ethylene is formed by overlap of the unhybridized p orbitals on the sp^2-hybrid carbon atoms. This overlap requires the two ends of the molecule to be coplanar.

Figure 8-2 shows that the two ends of the ethylene molecule cannot be twisted with respect to each other without disrupting the pi bond. Unlike single bonds, a carbon-carbon double bond does not permit rotation. This is the origin of cis-trans isomerism. If two groups are on the same side of a double bond (cis), they cannot rotate to opposite sides (trans) without breaking the pi bond. Figure 8-2 shows that there are two distinct isomers of 2-butene: *cis*-2-butene and *trans*-2-butene.

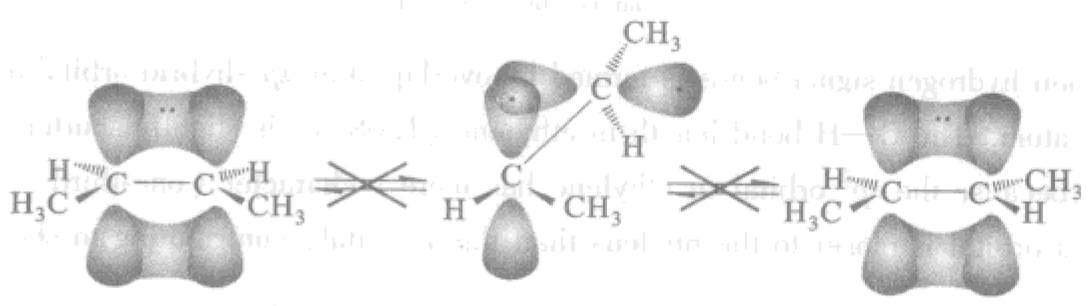
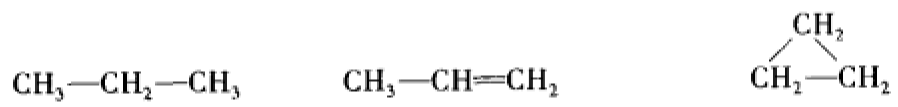


Figure 8-2 Distinct isomers resulting from carbon—carbon double bond. The two isomers of 2-butene cannot interconvert by rotation about the carbon-carbon double bond without breaking the pi bond.

8-3 Elements of Unsaturation

8-3A Elements of Unsaturation in Hydrocarbons

Alkenes are said to be **unsaturated** because they are capable of adding hydrogen in the presence of a catalyst. The product, an alkane, is called **saturated** because it cannot react with any more hydrogen. The presence of a pi bond of an alkene (or an alkyne) or the ring of a cyclic compound decreases the number of hydrogen atoms in a molecular formula. These structural features are called **elements of unsaturation** (*Degree of unsaturation* and *index of hydrogen deficiency* are equivalent terms). Each element of unsaturation corresponds to two fewer hydrogen atoms than in the "saturated" formula.



propane, C_3H_8 saturated; propene, C_3H_6 one element of unsaturation; cyclopropane, C_3H_6 one element of unsaturation

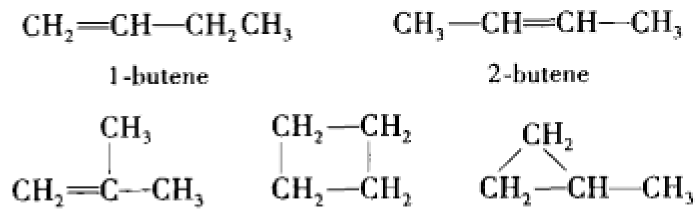
elements of unsaturation

$$= \frac{1}{2}(2C + 2 - H)$$

C = number of carbons

H = number of hydrogens

Consider, for example, the formula C_4H_8. A saturated alkane would have a $C_nH_{(2n+2)}$ formula, or C_4H_{10}. The formula C_4H_8 is missing two hydrogen atoms, so it has one element of unsaturation, either a pi bond or a ring. There are five constitutional isomers of formula C_4H_8:



1-butene; 2-butene; isobutylene; cyclobutane; methylcyclopropane

When you need a structure for a particular molecular formula, it helps to find the number of elements of unsaturation. Calculate the number of hydrogen atoms from the saturated formula, $C_nH_{(2n+2)}$, and see how many are missing. The number of elements of unsaturation is simply half the number of missing hydrogens. This simple calculation allows you to consider possible structures quickly, without always having to check for the correct molecular formula.

PROBLEM 8−1

Determine the number of elements of unsaturation in the molecular formula C_4H_6. Give all nine possible structures having this formula. Remember that

a double bond = one element of unsaturation

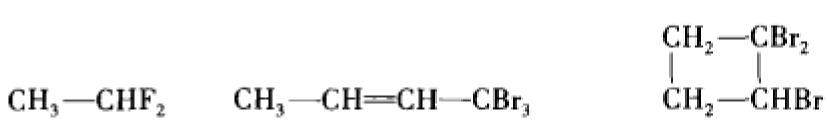
a ring = one element of unsaturation

a triple bond = two elements of unsaturation

8−3B Elements of Unsaturation with Heteroatoms

Heteroatoms (*hetero*, "different") are any atoms other than carbon and hydrogen. The rule for calcula-ting elements of unsaturation in hydrocarbons can be extended to include heteroatoms. Let's consider how the addition of a heteroatom affects the number of hydrogen atoms in the formula.

Halogens Halogens simply substitute for hydrogen atoms in the molecular formula. The formula C_2H_6 is saturated, so the formula $C_2H_4F_2$ is also saturated. C_4H_8 has one element of unsaturation, and $C_4H_5Br_3$ also has one element of unsaturation. In calculating the number of elements of unsaturation, simply *count halogens as hydrogen atoms*.

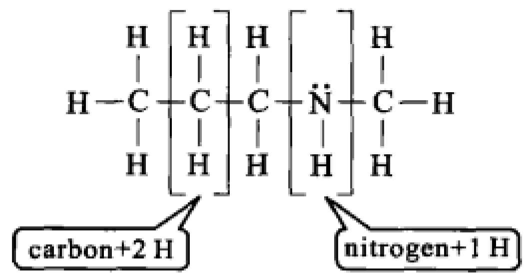


$C_2H_4F_2$ saturated; $C_4H_5Br_3$ one element of unsaturation; $C_4H_5Br_3$ one element of unsaturation

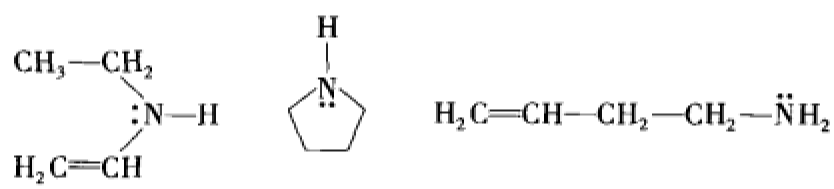
Oxygen An oxygen atom can be added to the chain without changing the number of hydrogen atoms or carbon atoms. In calculating the number of elements of unsaturation, *ignore the oxygen atoms*.

C_2H_6, saturated C_2H_6O, saturated C_2H_4O, one element of unsaturation

Nitrogen A nitrogen atom can take the place of a carbon atom in the chain, but nitrogen is trivalent, having only one additional hydrogen atom, compared with two hydrogens for each additional carbon atom. In computing the elements of unsaturation, *count nitrogen as half a carbon atom.*



The formula C_4H_9N is like a formula with $4\frac{1}{2}$ carbon atoms, with saturated formula $C_{4.5}H_{9+2}$. The formula C_4H_9N has one element of unsaturation, because it is two hydrogen atoms short of the saturated formula.



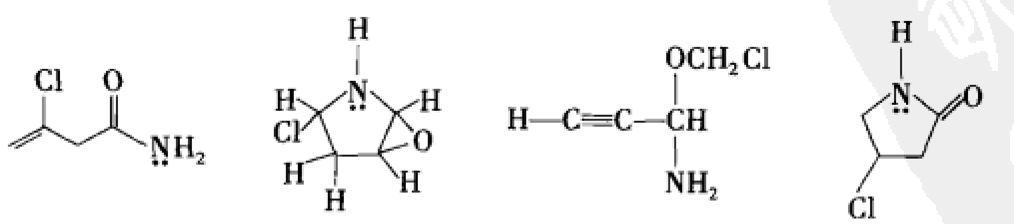
examples of formula C_4H_9N, one element of unsaturation

SOLVED PROBLEM 8-1

Draw at least four compounds of formula C_4H_6NOCl.

SOLUTION

Counting the nitrogen as $\frac{1}{2}$ carbon, ignoring the oxygen, and counting chlorine as a hydrogen shows the formula is equivalent to $C_{4.5}H_7$. The saturated formula for 4.5 carbon atoms is $C_{4.5}H_{11}$, so C_4H_6NOCl has two elements of unsa-turation. These could be two double bonds, two rings, one triple bond, or a ring and a double bond. There are many possibilities, four of which are listed here.



two double bonds two rings one triple bond one ring, one double bond

PROBLEM 8-2

For each of the following molecular formulas, determine the number of elements of unsaturation, and give three examples.

(**a**) $C_3H_4Cl_2$ (**b**) C_4H_8O (**c**) $C_4H_4O_2$ (**d**) $C_5H_5NO_2$ (**e**) C_6H_3NClBr

8-4 Commercial Importance of Alkenes

Because the carbon-carbon double bond is readily converted to other functional groups, alkenes are important intermediates in the synthesis of polymers, drugs, pesticides, and other valuable chemicals.

Ethylene is the organic compound produced in the largest volume, at around 158 billion pounds[①] per year worldwide. Most of this ethylene is polymerized to form 85 billion pounds of polyethylene per year. The remainder is used to synthesize a wide variety of organic chemicals including ethanol, acetic acid, ethylene glycol, and vinyl chloride (Figure 8-3). Ethylene also serves as a plant hormone, accelerating the ripening of fruit. For example, tomatoes are harvested and shipped while green, then treated with ethylene to make them ripen and turn red just before they are placed on display.

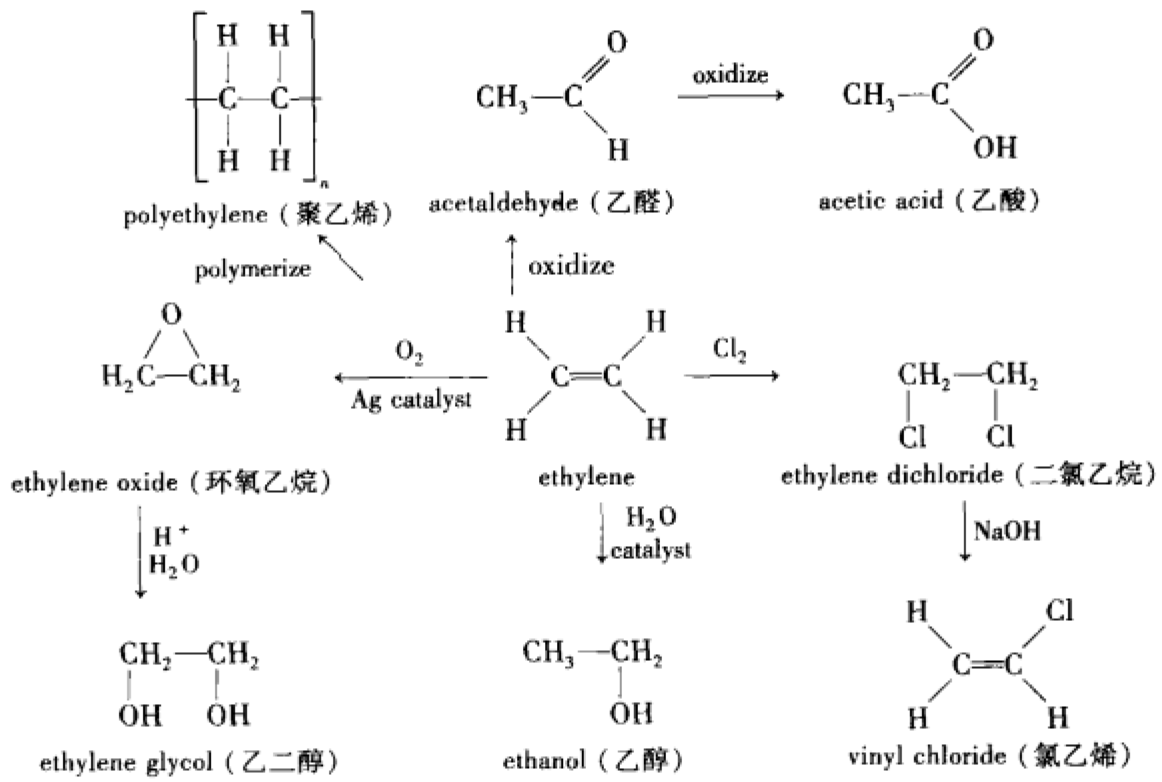


Figure 8-3 Uses of ethylene. Ethylene is the largest-volume industrial organic chemical. Most of the 158 billion pounds produced each year is polymerized to make polyethylene. Much of the rest is used to produce a variety of useful 2-carbon compounds.

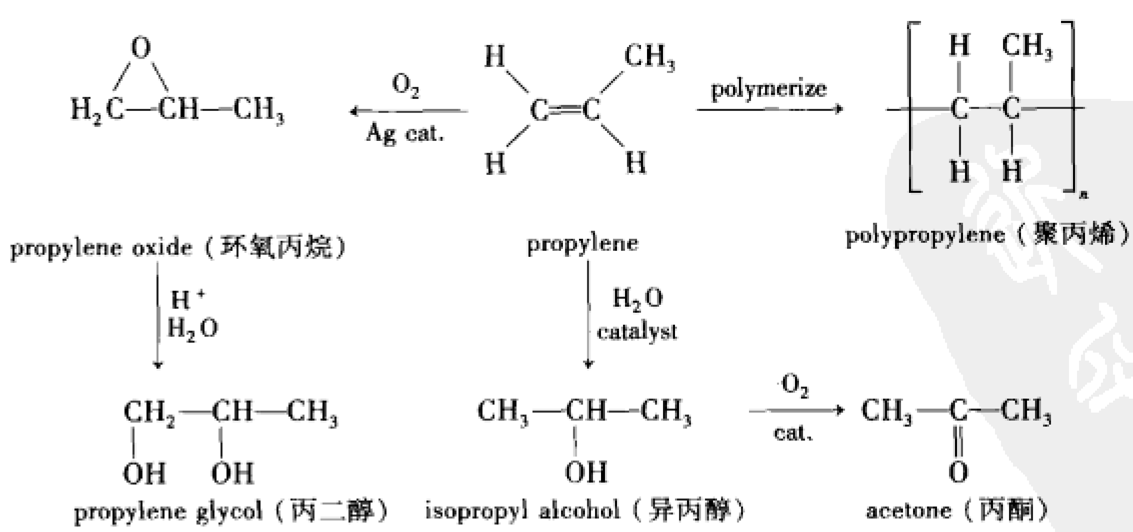


Figure 8-4 Uses of propylene. Most propylene is polymerized to make polypropylene. It is also used to make several important 3-carbon compounds.

① 1 pound = 0.453 6 kg。

Propylene is produced at the rate of about 86 billion pounds per year worldwide, with much of that going to make about 40 billion pounds of polypropylene. The rest is used to make propylene glycol, acetone, isopropyl alcohol, and a variety of other useful organic chemicals (Figure 8-4).

8-5 Stability of Alkenes

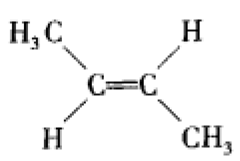
In making alkenes, we often find that the major product is the most stable alkene. Many reactions also provide opportunities for double bond to rearrange to more stable isomers. Therefore, we need to know how the stability of an alkene depends on its structure. Stabilities can be compared by converting diffe-rent compounds to a common product and comparing the amounts of heat given off. One possibility would be to measure heats of combustion from converting alkenes to CO_2 and H_2O. Heats of combustion are large numbers (several hundred kilocalories per mole), however, and measuring small differences in these large numbers is difficult. Instead, alkene energies are often compared by measuring the **heat of hydrogenation**: the heat given off ($\Delta H^{\ominus}$) during catalytic hydrogenation. Heats of hydrogenation can be measured about as easily as heats of combustion, yet they are smaller numbers and provide more accurate energy differences.

8-5A Heats of Hydrogenation

When an alkene is treated with hydrogen in the presence of a platinum catalyst, hydrogen adds to the double bond, reducing the alkene to an alkane. Hydrogenation is mildly exothermic, evolving about 80 to 120 kJ of heat per mole of hydrogen consumed. Consider the hydrogenation of 1-butene and *trans*-2-butene:

$$H_2C{=}CH{-}CH_2{-}CH_3 + H_2 \xrightarrow{Pt} CH_3{-}CH_2{-}CH_2{-}CH_3 \qquad \Delta H^{\ominus} = -126.8\ kJ/mol$$

1-butene (monosubstituted) → butane



$$+ H_2 \xrightarrow{Pt} CH_3{-}CH_2{-}CH_2{-}CH_3 \qquad \Delta H^{\ominus} = -115.5\ kJ/mol$$

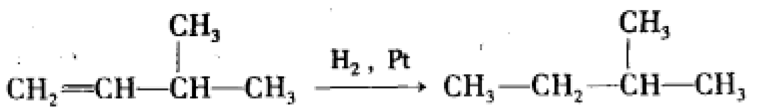
trans-2-butene (disubstituted) → butane

The difference in the stabilities of 1-butene and *trans*-2-butene is the difference in their heats of hydrogenation. *trans*-2-Butene is more stable by

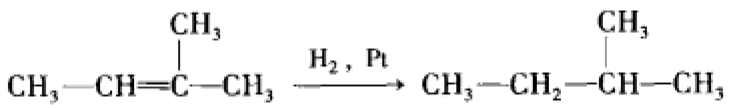
$$126.8\ kJ/mol - 115.5\ kJ/mol = 11.3\ kJ/mol$$

8-5B Substitution Effects

An 11.3 kJ/mol stability difference is typical between a monosubstituted alkene (1-butene) and a trans-disubstituted alkene (*trans*-2-butene). In the following equations, we compare the monosubstituted double bond of 3-methyl-1-butene with the trisubstituted double bond of 2-methyl-2-butene. The trisubstituted alkene is more stable by 14 kJ/mol.

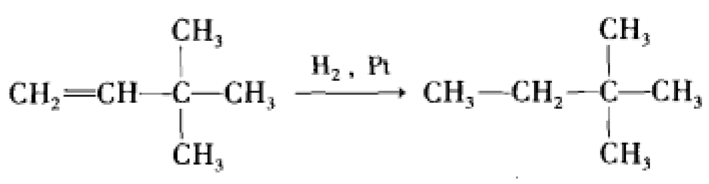


3-methyl-1-butene (monosubstituted) → 2-methylbutane $\Delta H^{\ominus} = -127$ kJ/mol



2-methyl-2-butene (trisubstituted) → 2-methylbutane $\Delta H^{\ominus} = -113$ kJ/mol

To be completely correct, we should compare heats of hydrogenation only for compounds that give the same alkane, as 3-methyl-1-butene and 2-methyl-2-butene do. Yet most alkenes with similar substitution patterns give similar heats of hydrogenation. For example, 3,3-dimethyl-1-butene (below) hydrogenates to give a different alkane than does 3-methyl-1-butene or 1-butene (above); yet these three monosubstituted alkenes have similar heats of hydrogenation because the alkanes formed have similar energies. In effect, the heat of hydrogenation is a measure of the energy content of the pi bond.



3,3-dimethyl-1-butene (monosubstituted) → 2,2-dimethylbutane $\Delta H^{\ominus} = -127$ kJ/mol

In practice, we can use heats of hydrogenation to compare the stabilities of different alkenes as long as they hydrogenate to give alkanes of similar energies. Most open-chain alkanes and unstrained cycloalkanes have similar energies, and we can use this approximation. Table 8-1 shows the heats of hydroge-nation of a variety of alkenes with different substitution. The compounds are ranked in decreasing order of their heats of hydrogenation, that is, from the least stable double bonds to the most stable. Note that the values are similar for alkenes with similar substitution patterns.

The most stable double bonds are those with the most alkyl groups attached. For example, hydrogenation of ethylene (no alkyl groups attached) evolves 137 kJ/mol, while propene and 1-pentene (one alkyl group for each) give off 126 kJ/mol. Double bonds with two alkyl groups hydrogenate to produce about 116—120 kJ/mol. Three or four alkyl substituents further stabilize the double bond, as with 2-methyl-2-butene (trisubstituted, 113 kJ/mol) and 2,3-dimethyl-2-butene (tetrasubstituted, 111 kJ/mol).

The values in Table 8-1 confirm **Zaitsev's rule (Saytzeff's rule)**:

More substituted double bonds are usually more stable.

In other words, the alkyl groups attached to the double-bonded carbons stabilize the alkene.

Two factors are probably responsible for the stabilizing effect of alkyl groups on a double bond. Alkyl groups are electron-donating, and they contribute electron density to the pi bond. In addition, bulky substituents like alkyl groups are best situated as far apart as possible. In an alkane, they are se-parated by the tetrahedral bond angle, about 109.5°. A double bond increases this separation to about 120°. In general, alkyl groups are separated best by the most highly substituted double bond. This ste-ric effect is illustrated in Figure 8-5 for two **double-bond isomers** (isomers that differ only in the position of the double bond). The isomer with the monosubstituted double bond separates the alkyl groups by only 109.5°, while the trisubstituted double bond separates them by about 120°.

TABLE 8-1 Molar Heats of Hydrogenation of Alkenes

Name	Chinese Name	Structure	Molar Heat of Hydrogenation ($-\Delta H^\ominus$) kJ	General Structure
ethene (ethylene)	乙烯	$H_2C{=}CH_2$	137	unsubstituted
propene (propylene)	丙烯	$CH_3{-}CH{=}CH_2$	126	monosubstituted $R{-}CH{=}CH_2$
1-butene	1-丁烯	$CH_3{-}CH_2{-}CH{=}CH_2$	127	
1-pentene	1-戊烯	$CH_3{-}CH_2{-}CH_2{-}CH{=}CH_2$	126	
1-hexene	1-己烯	$CH_3{-}(CH_2)_3{-}CH{=}CH_2$	126	
3-methyl-1-butene	3-甲基-1-丁烯	$(CH_3)_2CH{-}CH{=}CH_2$	127	
3,3-dimethyl-1-butene	3,3-二甲基-1-丁烯	$(CH_3)_3C{-}CH{=}CH_2$	127	
cis-2-butene	顺-2-丁烯	$(CH_3)(H)C{=}C(H)(CH_3)$ (CH₃ groups cis)	120	disubstituted (cis) $(R)(H)C{=}C(H)(R)$, R groups cis
cis-2-pentene	顺-2-戊烯	$(CH_3{-}CH_2)(H)C{=}C(H)(CH_3)$ (alkyl groups cis)	120	
2-methylpropene (isobutylene)	2-甲基丙烯(异丁烯)	$(CH_3)_2C{=}CH_2$	117	disubstituted (geminal) $R_2C{=}CH_2$
2-methyl-1-butene	2-甲基-1-丁烯	$CH_3{-}CH_2{-}C(CH_3){=}CH_2$	119	
2,3-dimethyl-1-butene	2,3-二甲基-1-丁烯	$(CH_3)_2CH{-}C(CH_3){=}CH_2$	117	
trans-2-butene	反-2-丁烯	$(CH_3)(H)C{=}C(H)(CH_3)$ (CH₃ groups trans)	116	disubstituted (trans) $(R)(H)C{=}C(H)(R)$, R groups trans
trans-2-pentene	反-2-戊烯	$(CH_3{-}CH_2)(H)C{=}C(H)(CH_3)$ (alkyl groups trans)	116	
2-methyl-2-butene	2-甲基-2-丁烯	$CH_3{-}C(CH_3){=}CH{-}CH_3$	113	trisubstituted $R_2C{=}CHR$
2,3-dimethyl-2-butene	2,3-二甲基-2-丁烯	$(CH_3)_2C{=}C(CH_3)_2$	111	tetrasubstituted $R_2C{=}CR_2$

Note: A lower heat of hydrogenation corresponds to lower energy and greater stability of the alkene.

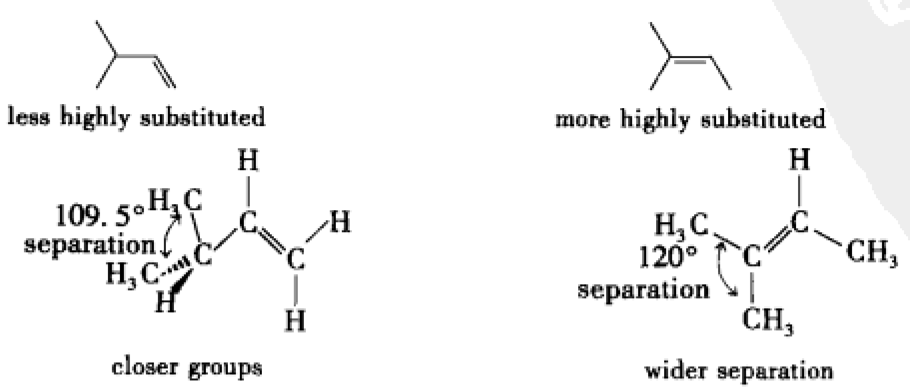
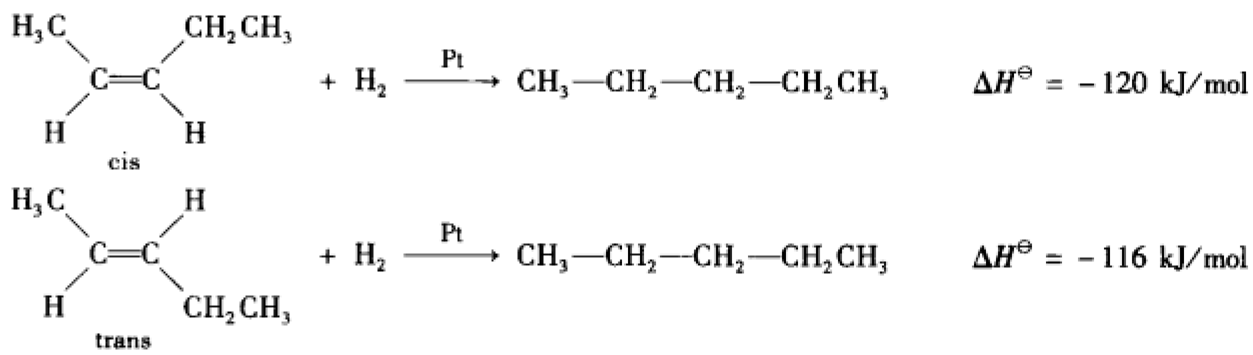


Figure 8−5 Bond angles in double-bond isomers. The isomer with the more highly substituted double bond has a larger angular separation between the bulky alkyl groups.

8-5C Energy Differences in cis-trans Isomers

The heats of hydrogenation in Table 8-1 show that trans isomers are generally more stable than the corresponding cis isomers. This trend seems reasonable because the alkyl substituents are separated farther in trans isomers than they are in cis isomers. The greater stability of the trans isomer is evident in the 2-pentenes, which show a 4 kJ/mol difference between the cis and trans isomers.



A 4 kJ/mol difference between cis and trans isomers is typical for disubstituted alkenes. Figure 8-6 summarizes the relative stabilities of alkenes, comparing them with ethylene, the least stable of the simple alkenes.

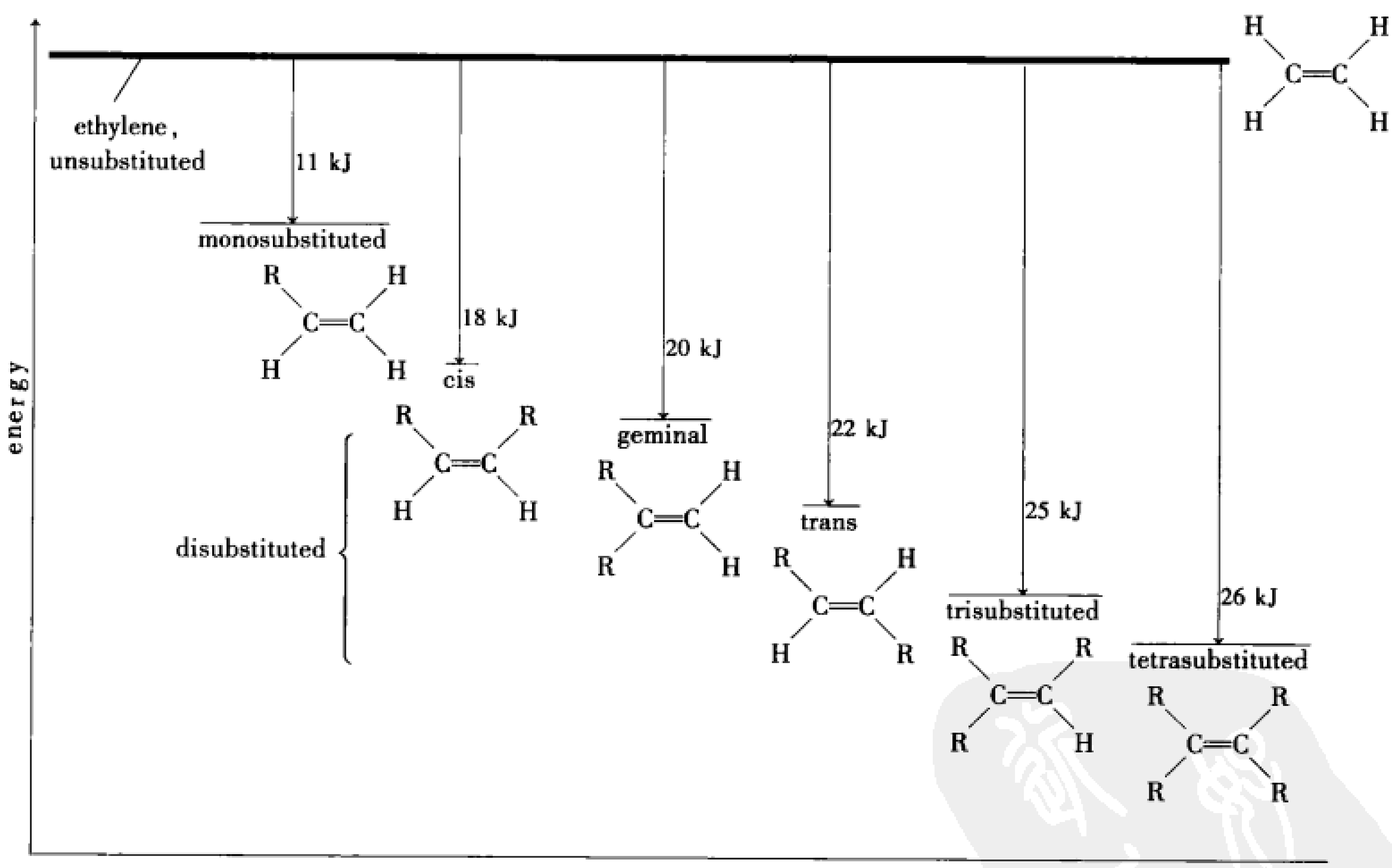


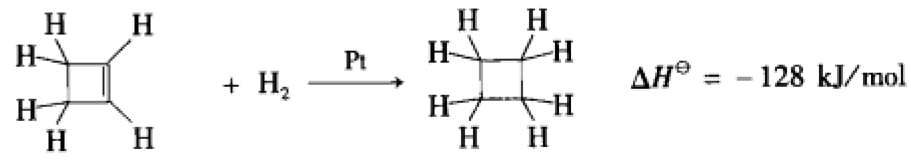
Figure 8-6 Relative energies of typical π bonds compared with ethylene. (The numbers are approximate.)

8-5D Stability of Cycloalkenes

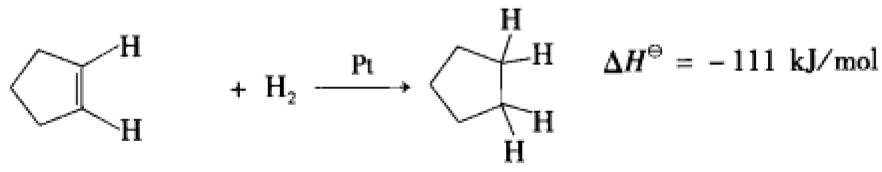
Most cycloalkenes react like acyclic (noncyclic) alkenes. The presence of a ring makes a major difference only if there is ring strain, either because of a small ring or because of a trans double bond. Rings that are five-membered or larger can easily accommodate double bonds, and these cycloalkenes react much like straight-chain al-

kenes. Three-and four-membered rings show evidence of ring strain, however.

Cyclobutene Cyclobutene has a heat of hydrogenation of −128 kJ/mol, compared with −111 kJ/mol for cyclopentene.



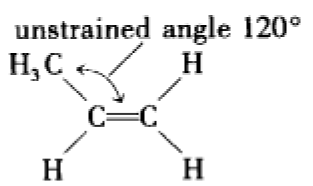
cyclobutene (环丁烯) cyclobutane



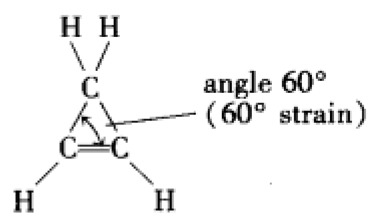
cyclopentene (环戊烯) cyclopentane

The double bond in cyclobutene has about 17 kJ/mol of *extra* ring strain (in addition to the ring strain in cyclobutane) by virtue of the small ring. The 90° bond angles in cyclobutene compress the angles of the sp^2-hybrid carbons (normally 120°) more than they compress the sp^3-hybrid angles (normally 109.5°) in cyclobutane. The extra ring strain in cyclobutene makes its double bond more reactive than a typical double bond.

Cyclopropene Cyclopropene has bond angles of about 60°, compressing the bond angles of the carbon-carbon double bond to half their usual value of 120°. The double bond in cyclopropene is highly strained.

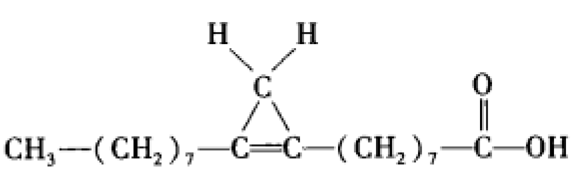


propene



cyclopropene (环丙烯)

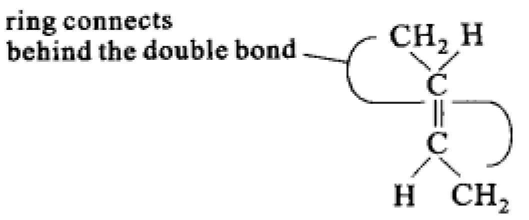
Many chemists once believed that a cyclopropene could never be made because it would snap open (or polymerize) immediately from the large ring strain. Cyclopropene was eventually synthesized, ho-wever, and it can be stored in the cold. Cyclopropenes were still considered to be strange, highly unusual compounds. Natural-product chemists were surprised when they found that the kernel oil of *Sterculia foelida*, a tropical tree, contains *sterculic acid*, a carboxylic acid with a cyclopropene ring.



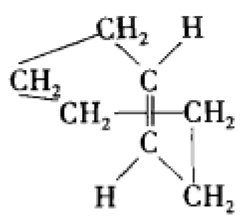
sterculic acid (苹婆酸)

Trans Cycloalkenes Another difference between cyclic and acyclic alkenes is the relationship between cis and trans isomers. In acyclic alkenes, the trans isomers are usually more stable; but the trans isomers of small cycloalkenes are rare, and those with fewer than eight carbon atoms are unstable at room temperature. The problem with making a trans cycloalkene lies in the geometry of the trans double bond. The two alkyl groups on a trans double bond are so far apart that several carbon atoms are needed to complete the ring.

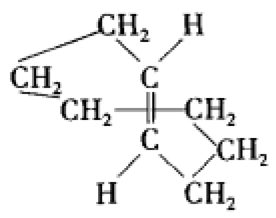
Try to make a model of *trans*-cyclohexene, being careful that the large amount of ring strain does not break your models. *trans*-Cyclohexene is too strained to be isolated, but *trans*-cycloheptene can be isolated at low temperatures. *trans*-Cyclooctene is stable at room temperature, although its cis isomer is still more stable.



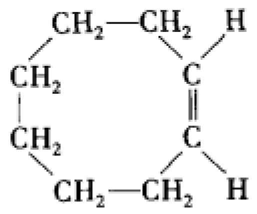
trans cyclic system



trans-cycloheptene
marginally stable

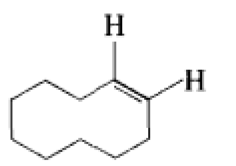


trans-cyclooctene
stable

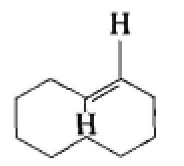


cis-cyclooctene
more stable

Once a cycloalkene contains at least ten or more carbon atoms, it can easily accommodate a trans double bond. For cyclodecene and larger cycloalkenes, the trans isomer is nearly as stable as the cis isomer.



cis-cyclodecene
(顺环癸烯)



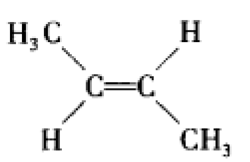
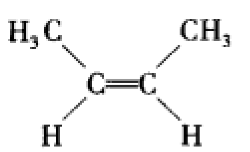
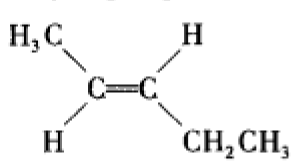
trans-cyclodecene
(反环癸烯)

8-6 Physical Properties of Alkenes

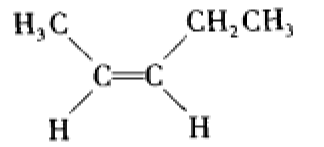
8-6A Boiling Points and Densities

Most physical properties of alkenes are similar to those of the corresponding alkanes. For example, the boiling points of 1-butene, *cis*-2-butene, *trans*-2-butene, and *n*-butane are all close to 0 ℃. Also like the alkanes, alkenes have densities around 0.6 or 0.7 g/cm^3. The boiling points and densities of some representative alkenes are listed in Table 8-2. The table shows that boiling points of alkenes increase smoothly with molecular weight. As with alkanes, increased branching leads to greater volatility and lower boiling points. For example, 2-methylpropene (isobutylene) has a boiling point of -7 ℃, which is lower than the boiling point of any of the unbranched butenes.

TABLE 8-2 Physical Properties of Some Representative Alkenes

Name	Structure	Carbons	Boiling Point/℃	Density/(g·cm^{-3})
ethene (ethylene)	$CH_2{=}CH_2$	2	-104	
propene (propylene)	$CH_3CH{=}CH_2$	3	-47	0.52
2-methylpropene (isobutylene)	$(CH_3)_2C{=}CH_2$	4	-7	0.59
1-butene	$CH_3CH_2CH{=}CH_2$	4	-6	0.59
trans-2-butene		4	1	0.60
cis-2-butene		4	4	0.62
3-methyl-1-butene	$(CH_3)_2CH{-}CH{=}CH_2$	5	25	0.65
1-pentene	$CH_3CH_2CH_2{-}CH{=}CH_2$	5	30	0.64
trans-2-pentene		5	36	0.65

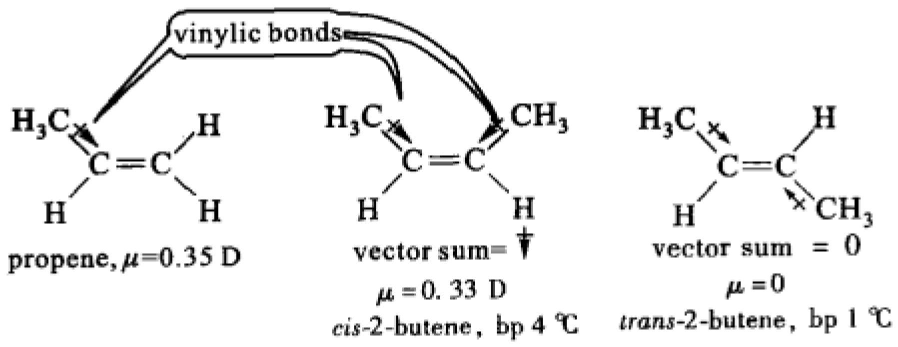
Continue

Name	Structure	Carbons	Boiling Point/℃	Density/($g \cdot cm^{-3}$)
cis-2-pentene		5	37	0.66
2-methyl-2-butene	$(CH_3)_2C{=}CH{-}CH_3$	5	39	0.66
1-hexene	$CH_3(CH_2)_3{-}CH{=}CH_2$	6	64	0.68
2,3-dimethyl-2-butene	$(CH_3)_2C{=}C(CH_3)_2$	6	73	0.71
1-heptene	$CH_3(CH_2)_4{-}CH{=}CH_2$	7	93	0.70
1-octene	$CH_3(CH_2)_5{-}CH{=}CH_2$	8	122	0.72
1-nonene	$CH_3(CH_2)_6{-}CH{=}CH_2$	9	146	0.73
1-decene	$CH_3(CH_2)_7{-}CH{=}CH_2$	10	171	0.74

8-6B Polarity

Like alkanes, alkenes are relatively nonpolar. They are insoluble in water but soluble in nonpolar solvents such as hexane, gasoline, halogenated solvents, and ethers. Alkenes tend to be slightly more polar than alkanes. however, for two reasons: The more weakly held electrons in the pi bond are more polarizable (contributing to instantaneous dipole moments), and the vinylic bonds tend to be slightly polar (contributing to a permanent dipole moment).

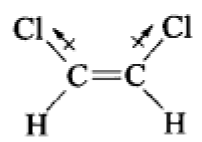
Alkyl groups are slightly electron donating toward a double bond, helping to stabilize it. This donation slightly polarizes the vinylic bond, with a small partial positive charge on the alkyl group and a small negative charge on the double-bond carbon atom. For example, propene has a small dipole moment of 0.35 D.



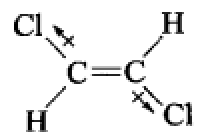
In a cis-disubstituted alkene, the vector sum of the two dipole moments is directed perpendicular to the double bond. In a trans-disubstituted alkene, the two dipole moments tend to cancel out. If an alkene is symmetrically trans disubstituted, the dipole moment is zero. For example, *cis*-2-butene has a nonzero dipole moment, but *trans*-2-butene has no measurable dipole moment.

Compounds with permanent dipole moments engage in dipole-dipole attractions, while those wit-hout permanent dipole moments engage only in van der Waals attractions. *cis*-2-Butene and *trans*-2-butene have similar van der Waals attractions, but only the cis isomer has dipole-dipole attractions. Because of its increased intermolecular attractions, *cis*-2-butene must be heated to a slightly higher temperature (4 ℃ versus 1 ℃) before it begins to boil.

The effect of bond polarity is even more apparent in the 1,2-dichloroethenes, with their strongly polar carbon-chlorine bonds. The cis isomer has a large dipole moment (2.4 D), giving it a boiling point 12 degrees higher than the trans isomer, with zero dipole moment.



cis
vector sum= ↕
μ=2.4 D
bp=60℃



trans
vector sum=0
μ=0
bp=48℃

PROBLEM 8-3

For each pair of compounds, predict the one with a higher boiling point. Which compounds have zero dipole moments?

(a) *cis*-1,2-dichloroethene or *cis*-1,2-dibromoethene

(b) *cis*-or *trans*-2,3-dichloro-2-butene

(c) cyclohexene or 1,2-dichlorocyclohexene

8-7 Alkene Synthesis by Elimination of Alkyl Halides

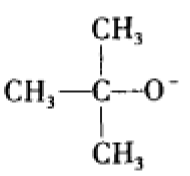
Dehydrohalogenation is the elimination of a hydrogen and a halogen from an alkyl halide to form an alkene. In Sections 7-16 through 7-20 we saw how dehydrohalogenation can take place by the E1 and E2 mechanisms. The second-order elimination (E2) is usually better for synthetic purposes because the E1 has more competing reactions.

8-7A Dehydrohalogenation by the E2 Mechanism

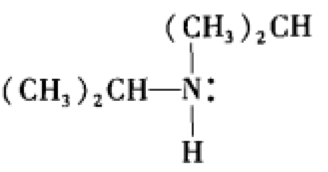
Second-order elimination is a reliable synthetic reaction, especially if the alkyl halide is a poor S_N2 substrate. E2 dehydrohalogenation takes place in one step, in which a strong base abstracts a proton form one carbon atom as the leaving group leaves the adjacent carbon.

The E2 dehydrohalogenation gives excellent yields with bulky secondary and tertiary alkyl halides, such as *t*-butyl bromide in the preceding example. A strong base forces second-order elimination (E2) by abstracting a proton. The molecule's bulkiness hinders second-order substitution (S_N2), and a relatively pure elimination product results. Tertiary halides are the best E2 substrates because they are prone to elimination and cannot undergo S_N2 substitution.

Use of a Bulky Base If the substrate is prone to substitution, a bulky base can minimize the amount of substitution. Large alkyl groups on a bulky base hinder its approach to attack a carbon atom (substitution), yet it can easily abstract a proton (elimination). Some of the bulky strong bases commonly used for elimination are *t*-butoxide ion, diisopropylamine, triethylamine, and 2,6-dimethylpyridine.



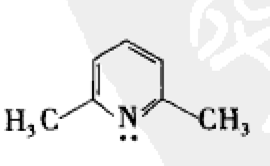
t-butoxide
(叔丁氧基负离子)



diisopropylamine
(二异丙基胺)

$(CH_3CH_2)_3N$:

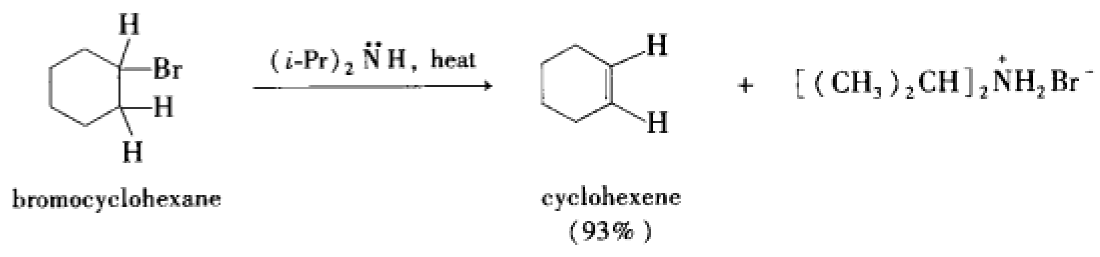
triethylamine
(三乙胺)



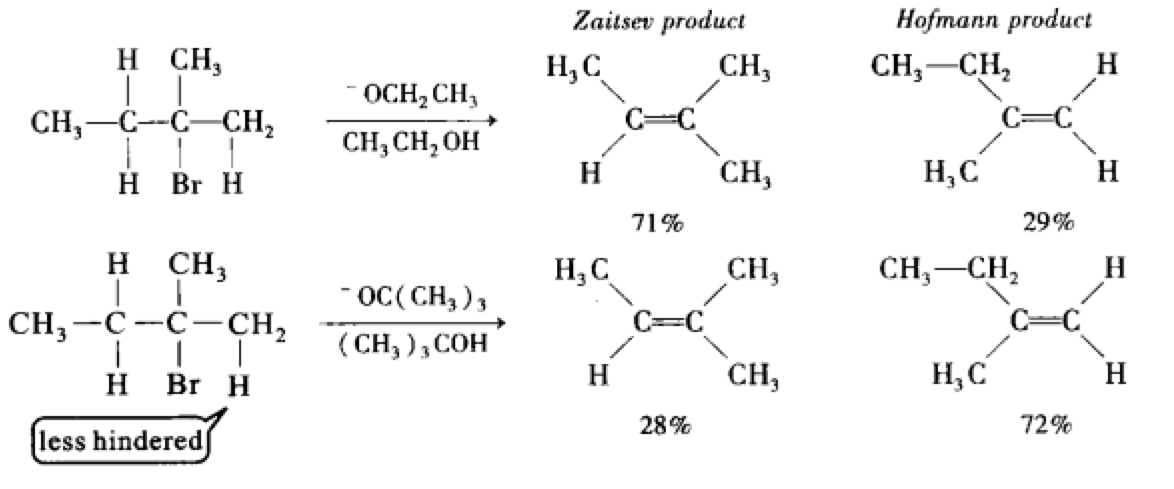
2,6-dimcthylpyridine
(2,6-二甲基吡啶)

The dehydrohalogenation of bromocyclohexane illustrates the use of a bulky base for elimination. Bromocyclohexane, a secondary alkyl halide, can undergo both substitution and elimination. Elimination (E2) is favored

over substitution (S_N2) by using a bulky base such as diisopropylamine. Diisopropy-lamine is too bulky to be a good nucleophile, but it acts as a strong base to abstract a proton.



Formation of the Hofmann Product Bulky bases can also accomplish dehydrohalogenations that do not follow the Zaitsev rule. Steric hindrance often prevents a bulky base from abstracting the proton that leads to the most highly substituted alkene. In these cases, it abstracts a less hindered proton, often the one that leads to formation of the least highly substituted product, called the **Hofmann product**. The following reaction gives mostly the **Zaitsev product** with the relatively unhindered ethoxide ion, but mostly the Hofmann product with the bulky *t*-butoxide ion.



PROBLEM 8-4

For each reaction, decide whether substitution or elimination (or both) is possible, and predict the products you expect. Label the major products.

(a) 1-bromo-1-methylcyclohexane + NaOH in acetone

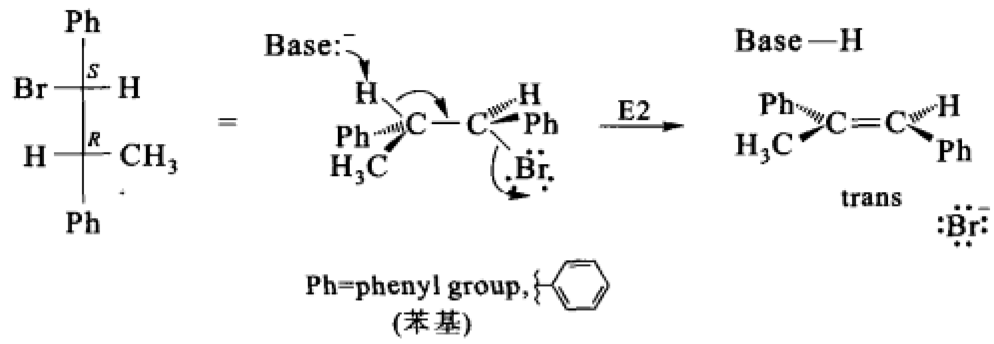
(b) 1-bromo-1-methylcyclohexane + triethylamine (Et_3N:)

(c) chlorocyclohexane + $NaOCH_3$ in CH_3OH

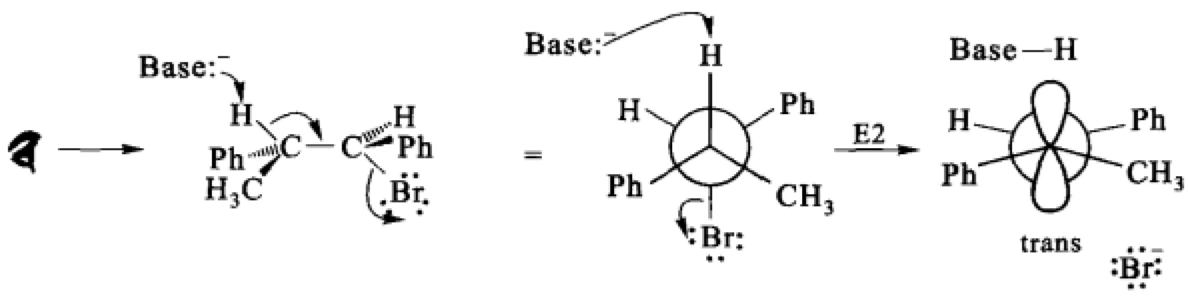
(d) chlorocyclohexane + $NaOC(CH_3)_3$ in $(CH_3)_3COH$

8-7B Stereospecific E2 Reactions

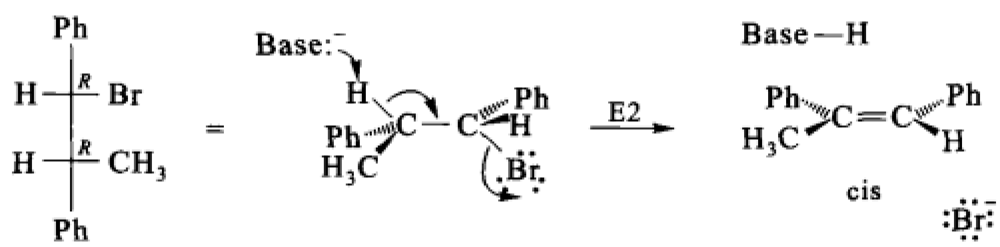
Like the S_N2 reaction (Section 7-11), the E2 is **stereospecific**: Different stereoisomers of the reactant give different stereoisomers of the product. The E2 is stereospecific because it normally goes through an anti and coplanar transition state. The products are alkenes, and different diastereomers of starting materials commonly give different diastereomers of alkenes. In Problem 7-25, you showed why the E2 elimination of one diastereomer of 1-bromo-1,2-diphenylpropane gives only the trans isomer of the alkene product.



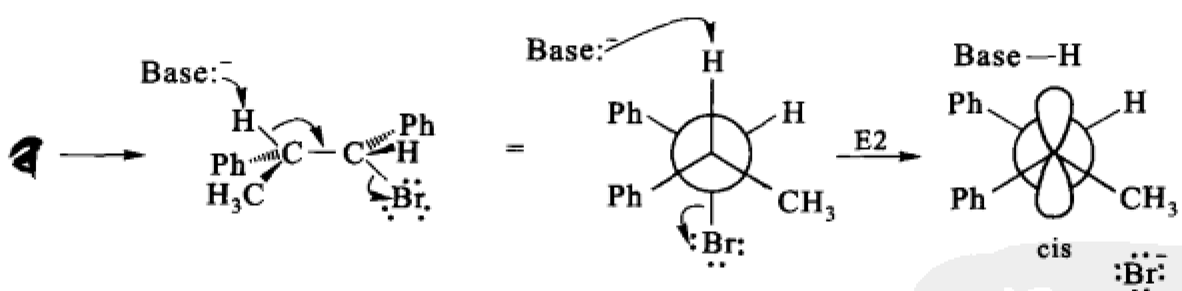
If we look at this reaction from the left end of the molecule, the anti and coplanar arrangement of the H and Br is apparent.



The following reaction shows how the anti-coplanar elimination of the other diastereomer (R, R) gives only the cis isomer of the product. In effect, the two different diastereomers of the reactant give two different diastereomers of the product: a stereospecific result.



Viewed from the left end of the molecule:

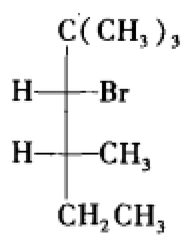


PROBLEM 8-5

Show that the (S,S) enantiomer of this second diastereomer of 1-bromo-1,2-diphenylpropane also undergoes E2 elimination to give the cis diastereomer of the product. (We do not expect these achiral reagents to distinguish between enan-tiomers.)

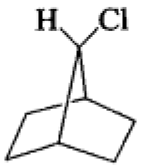
PROBLEM 8-6

Make models of the following compounds, and predict the products formed when they react with the strong bases shown.

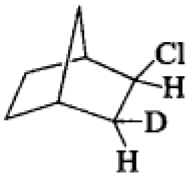
(a)  + KOH ⟶ (substitution and elimination)

(b) *meso*-1,2-dibromo-1,2-diphenylethane + $(CH_3CH_2)_3N$:

(c) (d, l)-1,2-dibromo-1,2-diphenylethane + $(CH_3CH_2)_3N$:

(d) 

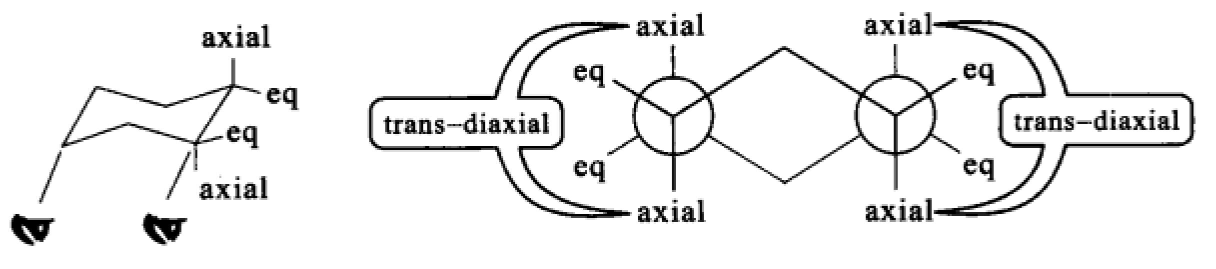
+ NaOH in acetone

(e) 

+ $(CH_3)_3C{-}O^-$ in $(CH_3)_3C{-}OH$

8–7C E2 Reactions in Cyclohexane Systems

Nearly all cyclohexanes are most stable in chair conformations. In the chair, all the carbon-carbon bonds are staggered, and any two adjacent carbon atoms have axial bonds in an anti-coplanar conformation, ideally oriented for the E2 reaction. (As drawn in the following figure, the axial bonds are vertical.) On any two adjacent carbon atoms, one has its axial bond pointing up and the other has its axial bond poin-ting down. These two bonds are trans to each other, and we refer to their geometry as **trans-diaxial.**



perspective view Newman projection

An E2 elimination can take place on this chair conformation only if the proton and the leaving group can get into a trans-diaxial arrangement. Figure 8–7 shows the E2 dehydrohalogenation of bromocyclohexane. The molecule must flip into the chair conformation with the bromine atom axial before elimination can occur.

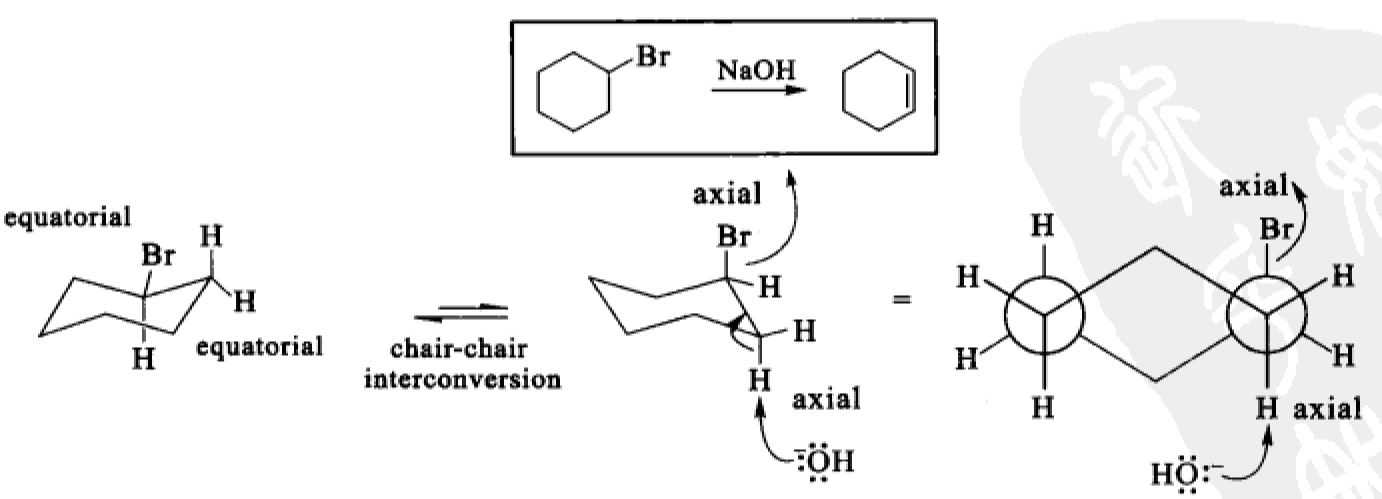
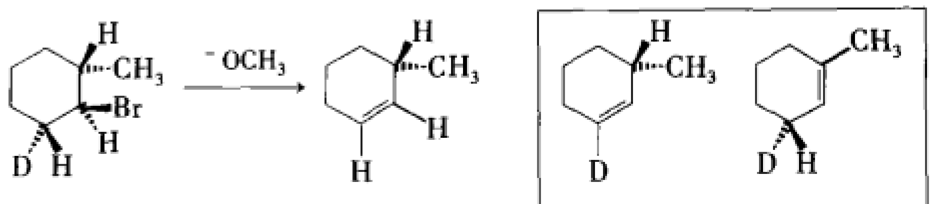


Figure 8–7 E2 eliminations on cyclohexane rings. E2 elimination of bromocyclohexane requires that both the proton and the leaving group be trans and both be axial.

PROBLEM 8-7

Explain why the following deuterated 1-bromo-2-methylcyclohexane undergoes dehydrohalogenation by the E2 mechanism, to give only the indicated product. Two other alkenes are not observed.



observed   not observed

PROBLEM 8-8

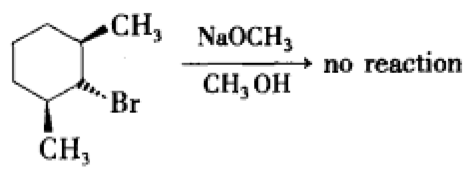
Predict the elimination products of the following reactions, and label the major products.

(**a**) *cis*-1-bromo-2-methylcyclohexane + $NaOCH_3$ in CH_3OH

(**b**) *trans*-1-bromo-2-methylcyclohexane + $NaOCH_3$ in CH_3OH

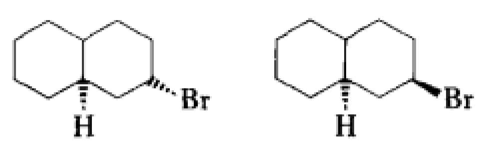
PROBLEM 8-9

When the following stereoisomer of 2-bromo-1,3-dimethylcyclohexane is treated with sodium methoxide, no E2 reaction is observed. Explain why this compound cannot undergo the E2 reaction in the chair conformation.



PROBLEM 8-10

Two stereoisomers of a bromodecalin are shown. Although the difference between these stereoisomers may seem trivial, one isomer undergoes elimination with KOH much faster than the other.



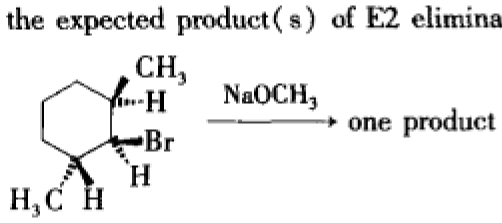
fast elimination   slow elimination

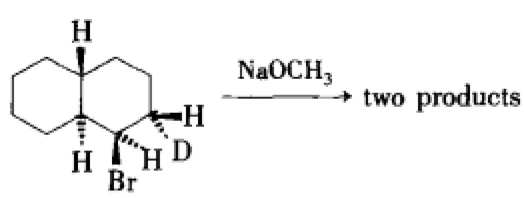
(**a**) Predict the products of these eliminations.

(**b**) Explain the large difference in the ease of elimination.

PROBLEM 8-11

Give the expected product(s) of E2 elimination for each reaction. (*Hint*: Use models!)

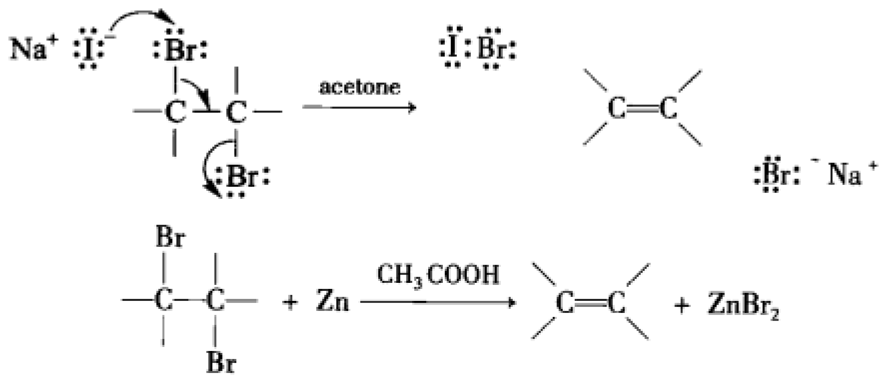
(**a**) 

(**b**) 

8-7D Debromination of Vicinal Dibromides

Vicinal dibromides (two bromines on adjacent carbon atoms) are converted to alkenes by reduction with either

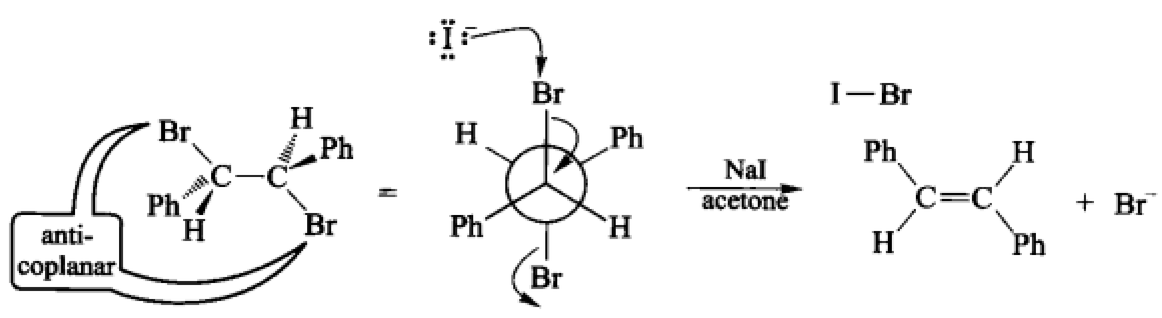
iodide ion in acetone or zinc in acetic acid. This **debromination** is rarely an important synthetic reaction, because the most likely origin of a vicinal dibromide is from bromination of an alkene. We discuss this reaction with dehydrohalogenation because the mechanisms are similar.



Debromination is formally a reduction because a molecule of Br_2 (an oxidizing agent) is removed. The reaction with iodide takes place by the E2 mechanism, with the same geometric constraints as the E2 dehydrohalogenation. Elimination usually takes place through an anti-coplanar arrangement, as shown in Mechanism 8-1, following. Acetone serves as a convenient solvent that dissolves most alkyl halides and sodium iodide.

MECHANISM 8-1 E2 Debromination of a Vicinal Dibromide

E2 debromination takes place by a concerted, stereospecific mechanism. Iodide ion removes one bromine atom, and the other bromine leaves as bromide ion.



meso-1,2-dibromo-1,2-diphenylethane

trans-stilbene (反-二苯乙烯)
(89%)

Use your models to show that only the trans isomer of stilbene is formed in this example by elimination through the anti-coplanar transition state.

Zinc serves as a reducing agent in zinc/acetic acid dehalogenation. The reaction is heterogeneous (part solid and part liquid), with the actual reduction taking place at the surface of the metallic zinc. Zinc is oxidized form the 0 oxidation state to the +2 oxidation state, forming $ZnBr_2$.

$$CH_3-\underset{Br}{\underset{|}{CH}}-\underset{Br}{\underset{|}{CH}}-CH_3 + Zn \xrightarrow{CH_3COOH} CH_3-CH=CH-CH_3 + ZnBr_2$$

PROBLEM 8-12

The preceding example shows *meso*-1,2-dibromo-1,2-diphenylethane reacting with iodide ion to give *trans*-stilbene. show how the other diastereomer of the starting material gives a different stereoisomer of the product.

PROBLEM 8-13

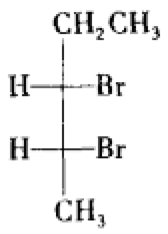
Show that the dehalogenation of 2,3-dibromobutane by iodide ion is stereospecific by showing that the two diastereomers of the starting material give different diastereomers of the product.

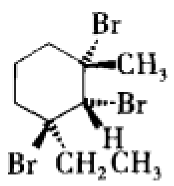
PROBLEM 8-14

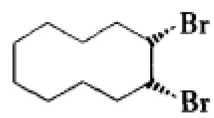
Predict the elimination products formed by debromination of the following compounds with iodide ion in acetone. Include stereochemistry, and give a correct name for each product.

(a) *trans*-1,2-dibromocyclohexane

(b) (3*R*,4*R*)-3,4-dibromoheptane

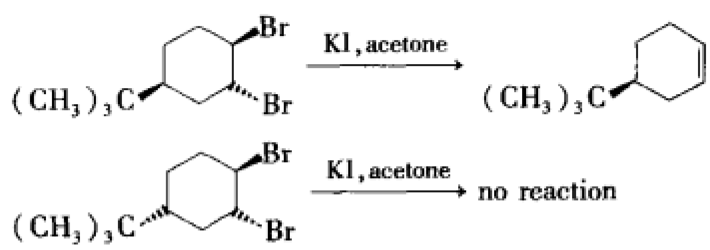
(c) 

(d) 

(e) 

PROBLEM 8-15

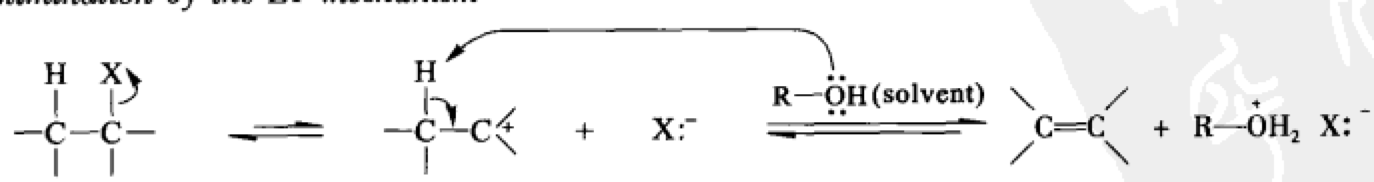
The following compounds show different rates of debromination. One reacts quite fast, and the other seems not to react at all. Explain this surprising difference in rates.



8-7E Dehydrohalogenation by the E1 Mechanism

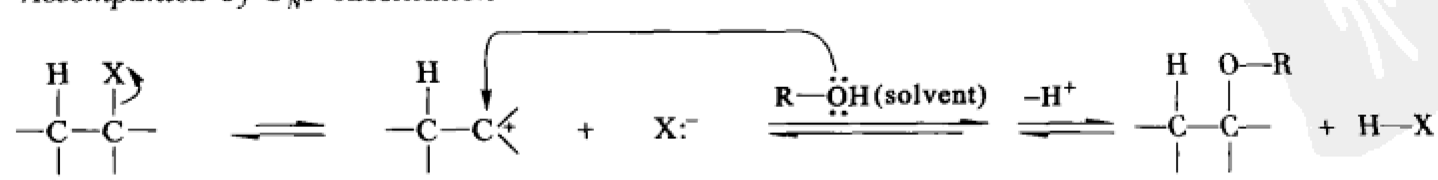
First-order dehydrohalogenation usually takes place in a good ionizing solvent (such as an alcohol or water), without a strong nucleophile or base to force second-order kinetics. The substrate is usually a se-condary or tertiary alkyl halide. First-order elimination requires ionization to from a carbocation, which loses a proton to a weak base (usually the solvent). E1 dehydrohalogenation is generally accompanied by S_N1 substitution, because the nucleophilic solvent can also attack the carbocation directly to form the substitution product.

Elimination by the E1 mechanism



formation of the carbocation — proton abstraction — elimination products

Accompanied by S_N1 substitution

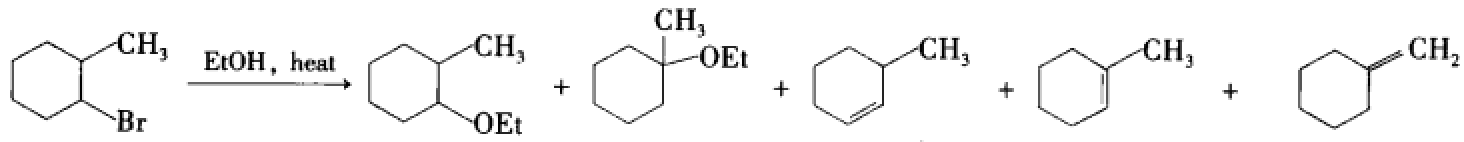


formation of the carbocation — nucleophilic attack — substitution products

Like all reactions involving carbocation intermediates, E1 dehydrohalogenations are prone to rearrangement, as shown in Problem 8-16.

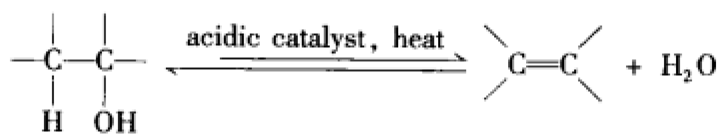
PROBLEM 8-16

Propose mechanisms for the following reactions.



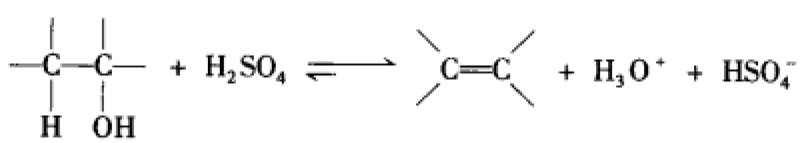
8-8 Alkene Synthesis by Dehydration of Alcohols

Dehydration of alcohols is a common method for making alkenes. The word *dehydration* literally means "removal of water."



Dehydration is reversible, and in most cases the equilibrium constant is not large. In fact, the reverse reaction (hydration) is a method for converting alkenes to alcohols (see Section 9-4). Dehydration can be forced to completion by removing the products from the reaction mixture as they form. The alkene boils at a lower temperature than the alcohol because the alcohol is hydrogen bonded. A carefully controlled distillation removes the alkene while leaving the alcohol in the reaction mixture.

Concentrated sulfuric acid and/or concentrated phosphoric acid are often used as reagents for dehydration because these acids act both as acidic catalysts and as dehydrating agents. Hydration of these acids is highly exothermic. The overall reaction (using sulfuric acid) is

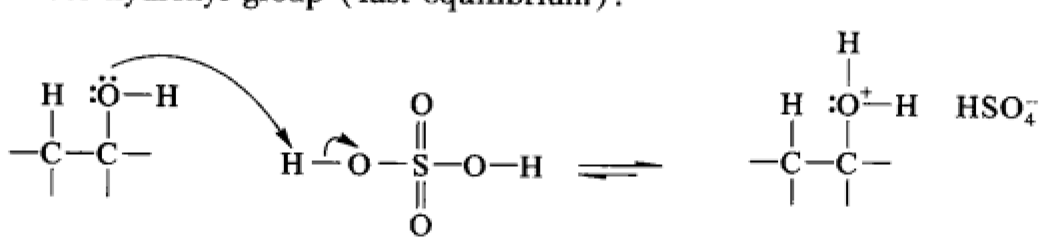


The mechanism of dehydration resembles the E1 mechanism introduced in Chapter 7 (Mechanism 7-7). The hydroxyl group of the alcohol is a poor leaving group (^-OH), but protonation by the acidic catalyst converts it to a good leaving group (H_2O). In the second step, loss of water from the protona-ted alcohol gives a carbocation. The carbocation is a very strong acid: Any weak base such as H_2O or HSO_4^- can abstract the proton in the final step to give the alkene.

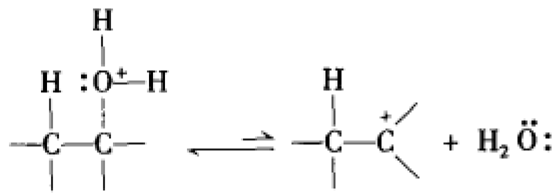
KEY MECHANISM 8-2 **Acid-Catalyzed Dehydration of an Alcohol**

Alcohol dehydrations usually involve E1 elimination of the protonated alcohol.

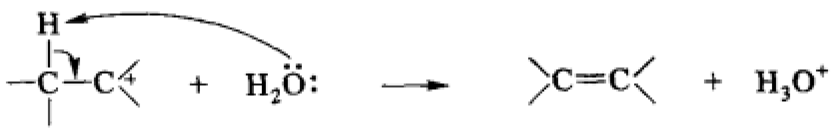
step 1: Protonation of the hydroxyl group (fast equilibrium).



step 2: Ionization to a carbocation (slow, rate limiting).



step 3: Deprotonation to give the alkene (fast).

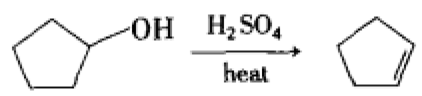


Like other E1 reactions, alcohol dehydration follows an order of reactivity that reflects carbocation stability: 3° alcohols react faster than 2° alcohols, and 1° alcohols are the least reactive. Rearrangements of the carbocation intermediates are common in alcohol dehydrations. In most cases, Zaitsev's rule applies: The major product is usually the one with the most substituted double bond.

PROBLEM 8-17

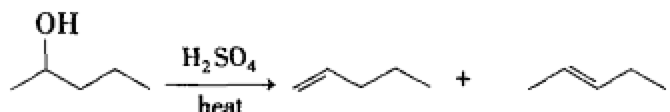
Propose mechanisms for the following reactions.

(a)



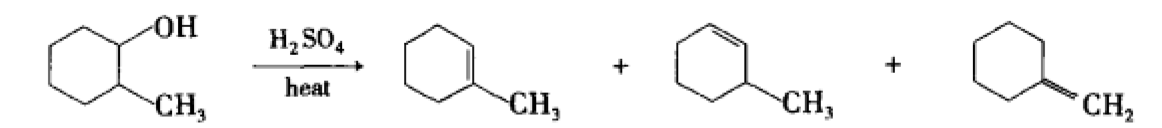
cyclopentanol cyclopentene

(b)



2-pentanol 1-pentene 2-pentene

(c)

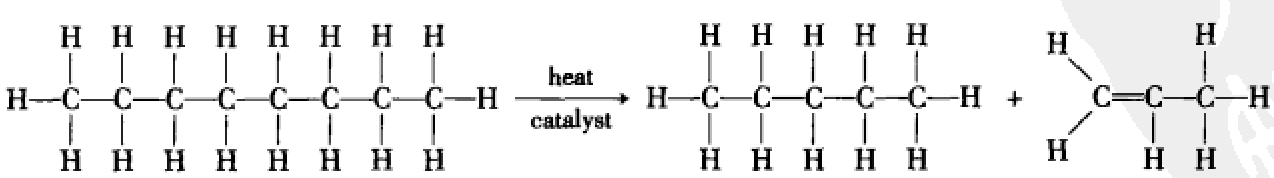


2-methylcyclohexanol 1-methylcyclohexene 3-methylcyclohexene methylenecyclohexane (亚甲基环己烷)

8-9 Alkene Synthesis by High-Temperature Industrial Methods

8-9A Catalytic Cracking of Alkanes

The least expensive way to make alkenes on a large scale is by the **catalytic cracking** of petroleum: hea-ting a mixture of alkanes in the presence of a catalyst (usually aluminosilicates). Alkenes are formed by bond cleavage to give an alkene and a shortened alkane.



long-chain alkane shorter alkane alkene

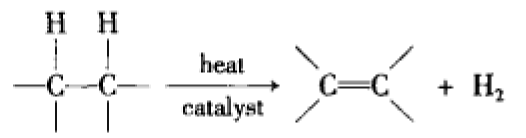
Cracking is used primarily to make small alkenes, up to about six carbon atoms. Its value depends on having a

market for all the different alkenes and alkanes produced. The average molecular weight and the relative amounts of alkanes and alkenes can be controlled by varying the temperature, catalyst, and concentration of hydrogen in the cracking process. A careful distillation on a huge column separates the mixture into its pure components, ready to be packaged and sold.

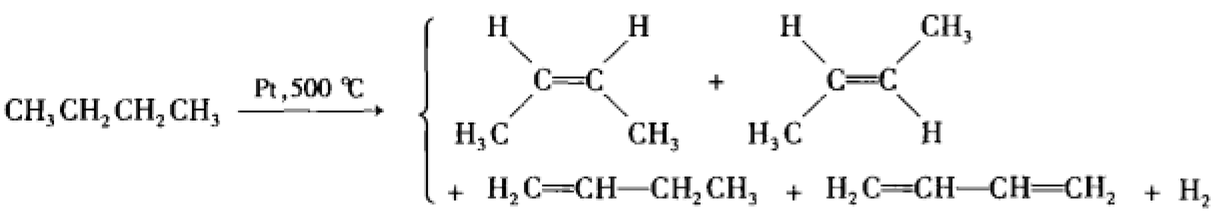
Because the products are always mixtures, catalytic cracking is not suitable for laboratory synthesis of alkenes. Better methods are available for synthesizing relatively pure alkenes from a variety of other functional groups.

8−9B Dehydrogenation of Alkanes

Dehydrogenation is the removal of H_2 from a molecule, just the reverse of hydrogenation. Dehydrogenation of an alkane gives an alkene. This reaction has an unfavorable enthalpy change but a favorable entropy change.



$\Delta H^{\ominus}$ = + 80 to + 120 kJ $\Delta S^{\ominus}$ = + 125 J/(mol·K)



The hydrogenation of alkenes is exothermic, with values of $\Delta H^{\ominus}$ around −80 to −120 kJ/mol. Therefore, dehydrogenation is endothermic and has an unfavorable (positive) value of $\Delta H^{\ominus}$. The entropy change for dehydrogenation is strongly favorable [$\Delta S^{\ominus}$ = +120 J/(mol·K)], however, because one alkane molecule is converted into two molecules (the alkene and hydrogen), and two molecules are more disordered than one.

The equilibrium constant for the hydrogenation-dehydrogenation equilibrium depends on the change in free energy, $\Delta G = \Delta H - T\Delta S$. At room temperature, the enthalpy term predominates and hydrogenation is favored. When the temperature is raised, however, the $(-T\Delta S)$ entropy term becomes larger and eventually dominates the expression. At a sufficiently high temperature, dehydrogenation is favored.

PROBLEM 8−18

The dehydrogenation of butane to *trans*−2−butene has $\Delta H^{\ominus}$ = +116 kJ/mol and $\Delta S^{\ominus}$ = +117 J/(mol·K).

(a) Compute the value of $\Delta G^{\ominus}$ for dehydrogenation at room temperature (25 ℃ or 298 K). Is dehydrogenation favored or disfavored?

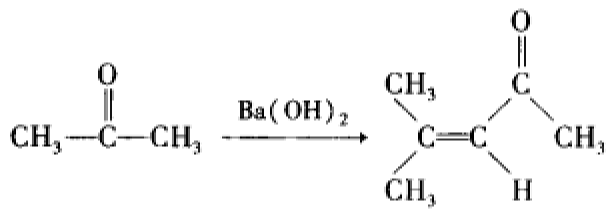
(b) Compute the value of ΔG for dehydrogenation at 1000 ℃, assuming ΔS and ΔH are constant. Is dehydrogenation favored or disfavored?

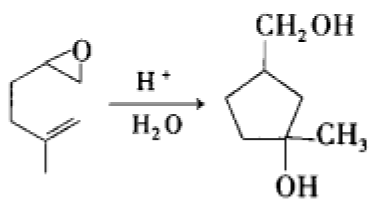
In many ways, dehydrogenation is similar to catalytic cracking. In both cases, a catalyst is used to lower the activation energy, and both reactions use high temperatures to increase a favorable entropy term $(-T\Delta S)$ and overcome an unfavorable enthalpy term (ΔH). Unfortunately, dehydrogenation and catalytic cracking also share a tendency to produce mixtures of products, and neither reaction is well suited for laboratory synthesis of alkenes.

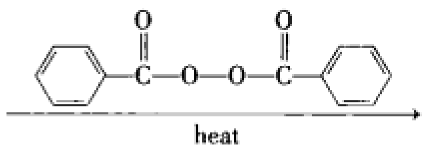
PROBLEM 8–19

For practice in recognizing mechanisms, classify each reaction according to the type of mechanism you expect:

1. Free-radical chain reaction
2. Reaction involving strong bases and strong nucleophiles
3. Reaction involving strong acids and strong electrophiles

(a) 

(b) 

(c) styrene （苯乙烯）  polystyrene （聚苯乙烯）

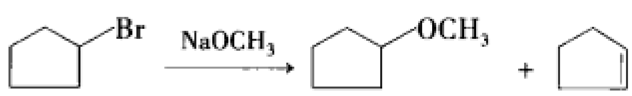
(d) ethylene （乙烯） $\xrightarrow{BF_3}$ polyethylene （聚乙烯）

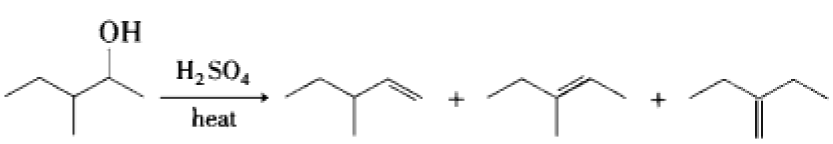
PROBLEM 8–20

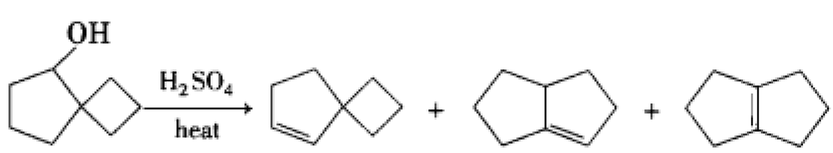
Propose mechanisms for the following reactions:

(a) $CH_3—CH_2—CH_2—CH_2—OH \xrightarrow{H_2SO_4,\ 140\ ℃} CH_3—CH{=}CH—CH_3$

(*Hint*: Hydride shift)

(b) 

(c) 

(d) 

Summary in Chinese

本 章 概 要

一、烯烃的结构

烯烃中双键碳原子为 sp^2 杂化，两个碳原子之间形成一个 $C(sp^2)—C(sp^2)\ \sigma$ 键，每个碳原子上有一个带单电子的未杂化的 $2p$ 轨道，当两个 $2p$ 轨道平行重叠时，可在碳碳间形成 π 键。此时，双键碳原子和与其连接的原子或基团处于同一平面。烯烃 π 键上的电子离原子核较远，易受环境影响发生极化，因此，容

易发生双键亲电加成、氧化和聚合等反应。尽管碳碳 π 键的键解离能明显小于碳碳 σ 键，室温下烯烃分子中两个双键碳原子不能以它们之间的 σ 键为轴自由旋转，旋转将会使 π 键断裂，由此导致烯烃存在顺反异构体。烯烃中的 C(sp^2)—H 键比烷烃中的 C(sp^3)—H 键稍强。由于烯烃具有 sp^2 杂化碳原子，除对称的反式烯烃外，烯烃的极性略大于烷烃。

二、烯烃的物理性质

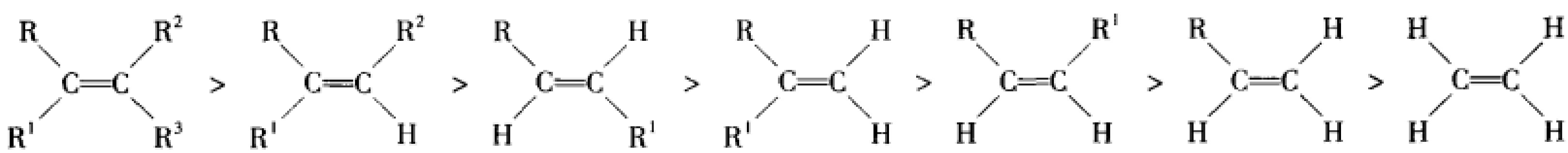
烯烃的沸点、相对密度和在水中的溶解度与烷烃相似。在同系列中，烯烃的沸点随相对分子质量增加而升高，正构烯烃的沸点高于同碳数带支链的烯烃。碳骨架相同的烯烃，双键由链端移向链中间时，烯烃的沸点、熔点都升高。由于烯烃反式异构体的极性通常小于相应的顺式异构体，相应地，其沸点比顺式异构体的沸点略低。

三、化合物的不饱和度

由于化合物中双键、三键和环的存在，而使分子式中氢原子数减少的这种结构特征被称为化合物的不饱和度(degree of unsaturation)或缺氢指数(index of hydrogen deficiency)。不饱和度可由下式计算：$(2N_C + 2 - N_H)/2$ (N_C 为分子式中碳原子数，N_H 为氢原子数)。计算不饱和度时不用考虑分子中的氧原子；当分子中有卤原子时，将卤原子看做氢原子来计算；当分子中有氮原子时，则不饱和度计算式应修正为：$(2N_C + 2 + N_N - N_H)/2$ (N_N 为分子式中氮原子数)。

四、烯烃的氢化焓与稳定性

烯烃加氢反应放出的热称为氢化焓，即一种烯烃与其相应的烷烃之间的能量差。氢化焓的大小反映了烯烃的稳定性。对于大多数链烯烃来说，双键碳原子上带烷基取代基越多，氢化焓绝对值越小，烯烃越稳定。此外，取代基的空间拥挤程度决定了反式烯烃比相应的顺式烯烃稳定。链烯烃的稳定性顺序如下：

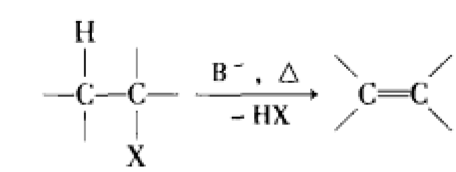


四取代 > 三取代 > 反式二取代 > 非对称二取代 > 顺式二取代 > 单取代 > 未取代

三元、四元环烯烃由于环张力非常不稳定，五元、六元环烯烃比正构链烯烃的稳定性好。当环大于 7 个碳原子时，反式环烯烃才能稳定存在。

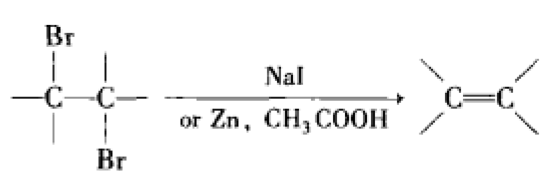
五、烯烃的制备(preparation of alkenes)

1. 卤代烷脱卤化氢反应(dehydrohalogenation of alkyl halides, Section 8-7)：



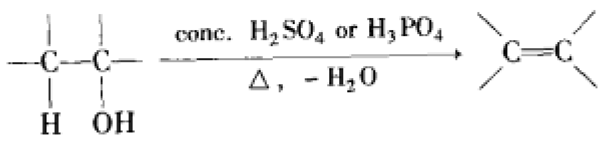
☆ E2 反应机理，一般情况下给出取代基多的烯烃(Zaitsev 规则)，但当卤代烷与体积大的碱反应时，取代基少的烯烃为主产物(Hofmann 规则)。反应起始物为伯卤代烷时，必须使用大体积强碱，才能发生 E2 消除，得到取代基少的烯烃。反应具有立体选择性，氢和卤原子为反式消除，能够从一种卤代烷的立体异构体出发选择性合成一种烯烃几何异构体。对于氢和卤原子处于重叠构象的刚性环来说，氢和卤原子为顺式消除。

2. 邻二溴脱卤反应(dehalogenation of vicinal dibromides, Section 8-7)：



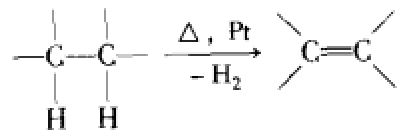
☆ E2 反应机理，两个溴原子为反式消除，一种邻二溴的立体异构体只给出一种烯烃几何异构体。

3. 酸催化醇脱水反应(acid-catalyzed dehydration of alcohols, Section 8-8)：



☆ E1 反应机理,经过碳正离子,应考虑碳正离子重排。取代基多的烯烃为主产物,如有顺反异构体,一般反式烯烃为主产物。

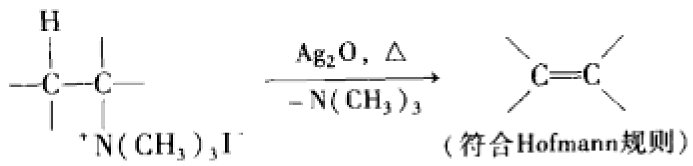
4. 烷烃脱氢反应(dehydrogenation of alkanes,Section 8−9):



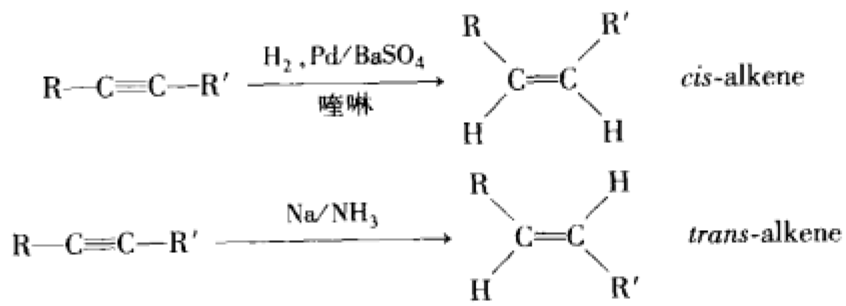
☆ 此法仅用于合成小分子烯烃,反应一般给出多种烯烃异构体的混合物。

以下三种可用于制备烯烃的反应将分别在第 10、19 和 20 章中介绍。

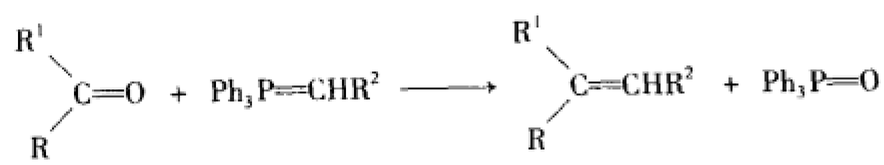
5. 霍夫曼和科普消除反应(Hofmann and Cope eliminations,Sections 20−13 and 20−14):



6. 炔烃还原反应(reduction of alkynes,Section 10−8):



7. 维蒂希反应(Wittig reaction,Section 19−14):



Essential Problem-Solving Skills in Chapter 8

1. Use heats of hydrogenation to compare stabilities of alkenes.
2. Predict relative stabilities of alkenes and cycloalkenes, based on structure and stereochemistry.
3. Predict the products of dehydrohalogenation of alkyl halides, dehalogenation of dibromides, and dehydration of alcohols, including major and minor products.
4. Propose logical mechanisms for dehydrohalogenation, dehalogenation, and dehydration reactions.
5. Predict and explain the stereochemistry of E2 eliminations to form alkenes. Predict E2 reactions on cyclohexane systems.
6. Propose effective single-step and multistep syntheses of alkenes.

Study Problems

8−21 Define each term and give an example.

(**a**) double-bond isomers(双键异构体) (**b**) Zaitsev elimination (**c**) element of unsaturation(不饱和元素)

(d) Hofmann product (e) hydrogenation（加氢反应） (f) dehydrogenation（脱氢反应）

(g) dehydrohalogenation（脱卤化氢） (h) dehydration（脱水反应） (i) dehalogenation（脱卤反应）

(j) geminal dihalide（偕碳二卤代物） (k) vicinal dihalide（邻二卤代物） (l) heteroatom（杂原子）

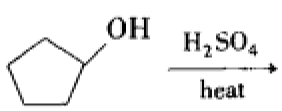
8-22 For each alkene, indicate the direction of the dipole moment. For each pair, determine which compound has the larger dipole moment.

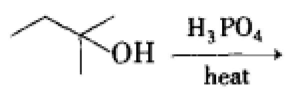
(a) *cis*-1,2-difluoroethene or *trans*-1,2-difluoroethene

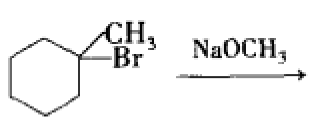
(b) *cis*-1,2-dibromoethene or *trans*-2,3-dibromo-2-butene

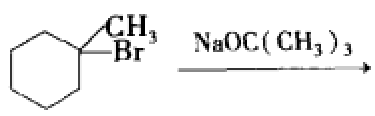
(c) *cis*-1,2-dibromo-1,2-dichloroethene or *cis*-1,2-dichloroethene

8-23 Predict the products of the following reactions. When more than one product is expected, predict which will be the major product.

(a) 

(b) 

(c) 

(d) 

8-24 Show how you would prepare cyclopentene from each compound.

(a) *trans*-1,2-dibromocyclopentane (b) cyclopentanol

(c) cyclopentyl bromide (d) cyclopentane (not by dehydrogenation)

8-25 Predict the products formed by sodium hydroxide-promoted dehydrohalogenation of the following compounds. In each case, predict which will be the major product.

(a) 1-bromobutane (b) 2-chlorobutane (c) 3-bromopentane

(d) 1-bromo-1-methylcyclohexane (e) *cis*-1-bromo-2-methylcyclohexane

(f) *trans*-1-bromo-2-methylcyclohexane

8-26 What halides would undergo dehydrohalogenation to give the following pure alkenes?

(a) 1-butene (b) isobutylene (c) 2-pentene

(d) methylenecyclohexane (e) 4-methylcyclohexene

8-27 In the dehydrohalogenation of alkyl halides, a strong base such as *t*-butoxide usually gives the best results via the E2 mechanism.

(a) Explain why a strong base such as *t*-butoxide cannot dehydrate an alcohol through the E2 mechanism.

(b) Explain why strong acid, used in the dehydration of an alcohol, is not effective in the dehydrohalogenation of an alkyl halide.

8-28 Predict the major products of acid-catalyzed dehydration of the following alcohols.

(a) 2-pentanol (b) 1-methylcyclopentanol

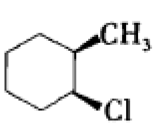
(c) 2-methylcyclohexanol (d) 2,2-dimethyl-1-propanol

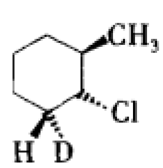
8-29 Predict the dehydrohalogenation product(s) that result when the following alkyl halides are heated in alcoholic KOH. When more than one product is formed, predict the major and minor products.

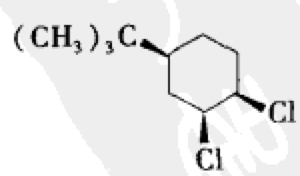
(a) $(CH_3)_2CH—C(CH_3)_2$ with Br on the second carbon (C)

(b) $(CH_3)_2CH—CH—CH_3$ with Br on the second CH

(c) $(CH_3)_2C—CH_2—CH_3$ with Br on the C

(d) 

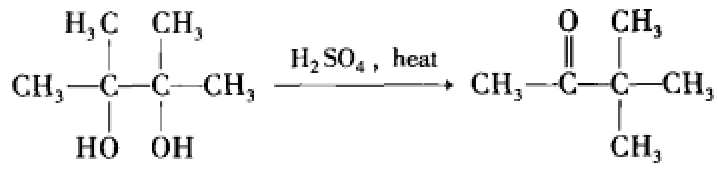
(e) 

(f) 

8-30 E1 eliminations of alkyl halides are rarely useful for synthetic purposes because they give mixtures of substitution and elimination products. Explain why the sulfuric acid-catalyzed dehydration of cyclohexanol gives a good yield of cyclohexene even though the reaction goes by an E1 mechanism. (*Hint*: What are the nucleophiles in the reaction mixture? What products are formed if these nucleophiles attack the carbocation? What further reactions can these substitution products undergo?)

***8-31** The following reaction is called the *pinacol rearrangement*. The reaction begins with an acid-promoted ionization to give a

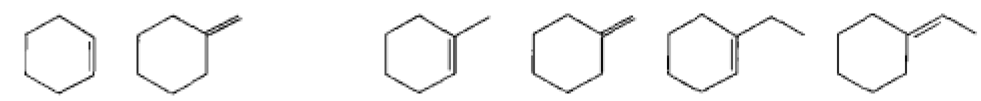
carbocation. This carbocation undergoes a methyl shift to give a more stable, resonance-stabilized cation. Loss of a proton gives the observed product. Propose a mechanism for the pinacol rearrangement.



pinacol   pinacolone

8−32 A chemist allows some pure (2*S*, 3*R*)-3-bromo-2, 3-diphenylpentane to react with a solution of sodium ethoxide ($NaOCH_2CH_3$) in ethanol. The products are two alkenes: **A** (cis-trans mixture) and **B**, a single pure isomer. Under the same conditions, the reaction of (2*S*,3*S*)-3-bromo-2,3-diphenylpentane gives two alkenes, **A** (cis-trans mixture) and **C**. Upon catalytic hydrogenation, all three of these alkenes (**A**, **B**, and **C**) give 2,3-diphenylpentane. Determine the structures of **A**, **B**, and **C**, give equations for their formation, and explain the stereospecificity of these reactions.

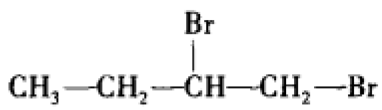
8−33 A double bond in a six-membered ring is usually more stable in an endocyclic position than in an exocyclic position. Hydrogenation data on two pairs of compounds follow. One pair suggests that the energy difference between endocyclic and exocyclic double bonds is about 9 kJ/mol. The other pair suggests an energy difference of about 5 kJ/mol. Which number do you trust as being more representative of the actual energy difference? Explain your answer.

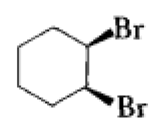


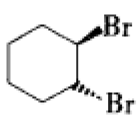
endocyclic (环内)   exocyclic (环外)   107   116   105   110

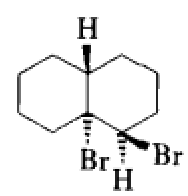
heats of hydrogenation/($kJ \cdot mol^{-1}$)

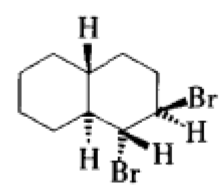
8−34 Predict the products of the following eliminations of vicinal dibromides with potassium iodide. Remember to consider the geometric constraints of the E2 reaction.

(a) 

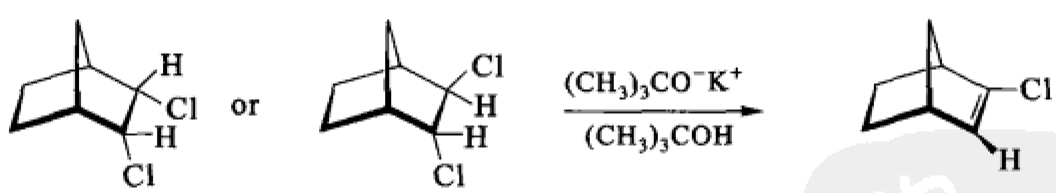
(b) 

(c) 

(d) 

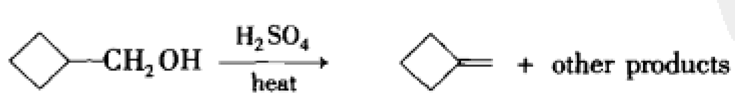
(e) 

***8−35** One of the following dichloronorbornanes undergoes elimination much faster than the other. Determine which one reacts faster, and explain the large difference in rates.



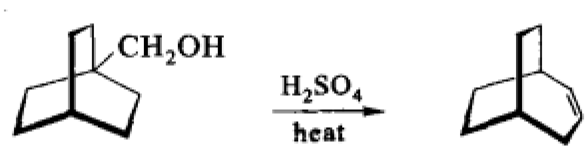
cis   trans

***8−36** A graduate student wanted to make methylenecyclobutane, and he tried the following reaction. Propose structures for the other products, and give mechanisms to account for their formation.



methylenecyclobutane (亚甲基环丁烷)
(minor)

***8−37** Give a mechanism to explain the formation of the following product. In your mechanism, explain the cause of the rearrangement, and explain the failure to form the Zaitsev product.

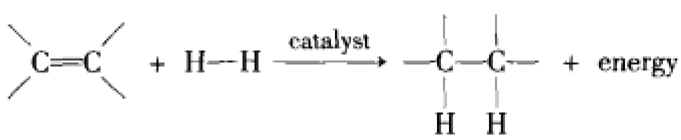


Chapter 9
Reactions of Alkenes

All alkenes have a common feature: a carbon-carbon double bond. The reactions of alkenes arise from the reactivity of the carbon-carbon double bond. Once again, the concept of the functional group helps to organize and simplify the study of chemical reactions. By studying the characteristic reactions of the double bond, we can predict the reactions of alkenes we have never seen before.

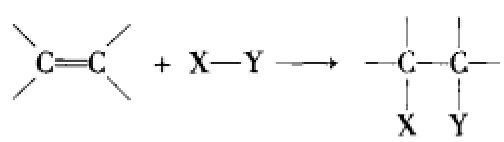
9-1 Reactivity of the Carbon-Carbon Double Bond

Because single bonds (sigma bonds) are more stable than pi bonds, the most common reactions of double bonds transform the pi bond into a sigma bond. For example, catalytic hydrogenation converts the C═C pi bond and the H—H sigma bond into two C—H sigma bonds (Section 8-5). The reaction is exothermic ($\Delta H^{\ominus}$ = about −80 to −120 kJ/mol), showing that the product is more stable than the reactants.

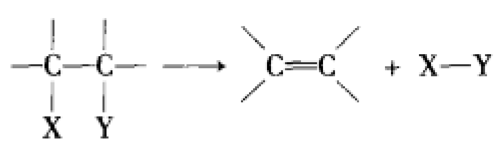


Hydrogenation of an alkene is an example of an **addition**, one of the three major reaction types we have studied: addition, elimination, and substitution. In an addition, two molecules combine to form one product molecule. When an alkene undergoes addition, two groups add to the carbon atoms of the double bond and the carbons become saturated. In many ways, addition is the reverse of **elimination**, in which one molecule splits into two fragment molecules. In a **substitution**, one fragment replaces another fragment in a molecule.

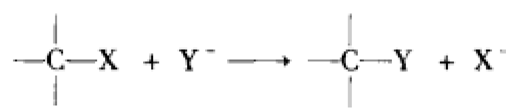
Addition
(加成反应)



Elimination
(消除反应)



Substitution
(取代反应)



Addition is the most common reaction of alkenes, and in this chapter we consider additions to alkenes in detail. A wide variety of functional groups can be formed by adding suitable reagents to the double bonds of alkenes.

9-2 Electrophilic Addition to Alkenes

In principle, many different reagents could add to a double bond to form more stable products; that is, the reactions are energetically favorable. Not all of these reactions have convenient rates, however. For example, the reaction of ethylene with hydrogen (to give ethane) is strongly exothermic, but the rate is very slow. A mixture of ethylene and hydrogen can remain for years without appreciable reaction. Adding a catalyst such as platinum, palladium, or nickel allows the reaction to take place at a rapid rate.

Some reagents react with carbon-carbon double bonds without the aid of a catalyst. To understand what types of reagents react with double bonds, consider the structure of the pi bond. Although the electrons in the sigma bond framework are tightly held, the pi bond is delocalized above and below the sigma bond. The pi-bonding electrons are spread farther from the carbon nuclei, and they are more loosely held. A strong electrophile has an affinity for these loosely held electrons; it can pull them away to form a new bond (Figure 9-1), leaving one of the carbon atoms with only three bonds and a positive charge: a carbocation. In effect, the double bond has reacted as a nucleophile, donating a pair of electrons to the electrophile.

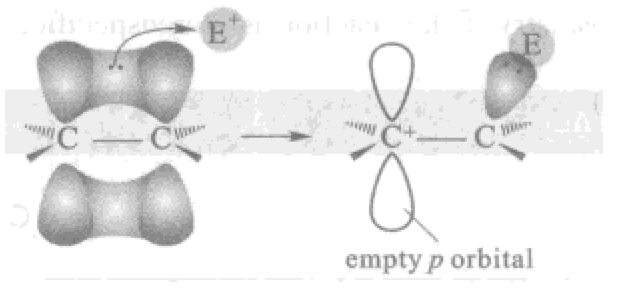


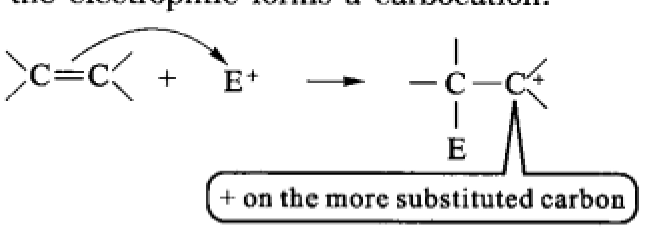
Figure 9-1 The pi bond as a nucleophile. A strong electrophile attracts the electrons out of the pi bond to form a new sigma bond, generating a carbocation. The curved arrow shows the movement of electrons, from the electron-rich pi bond to the electron-poor electrophile.

Most addition reactions involve a second step in which a nucleophile attacks the carbocation (as in the second step of the S_N1 reaction), forming a stable addition product. In the product, both the electrophile and the nucleophile are bonded to the carbon atoms that were connected by the double bond. This reaction is outlined in Key Mechanism Box 9-1, identifying the electrophile as E^+ and the nucleophile as Nuc$\bar{:}$. This type of reaction requires a strong electrophile to attract the electrons of the pi bond and generate a carbocation in the rate-limiting step. Most alkene reactions fall into this large class of **electrophilic additions** to alkenes.

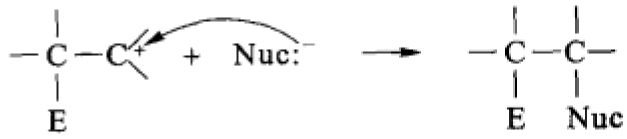
KEY MECHANISM 9-1 Electrophilic Addition to Alkenes

A wide variety of electrophilic additions involve similar mechanisms. First, a strong electrophile attracts the loosely held electrons from the pi bond of an alkene. The electrophile forms a sigma bond to one of the carbons of the (former) double bond, while the other carbon becomes a carbocation. The carbocation (a strong electrophile) reacts with a nucleophile (often a weak nucleophile) to form another sigma bond.

***Step 1*:** Attack of the pi bond on the electrophile forms a carbocation.



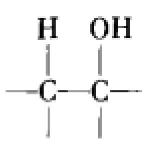
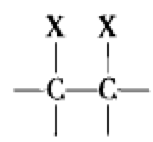
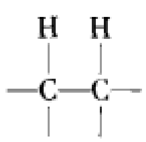
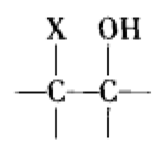
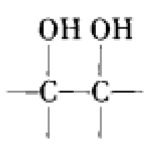
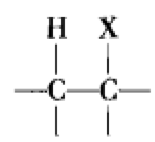
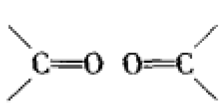
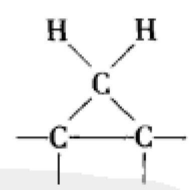
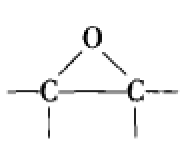
Step 2: Attack by a nucleophile gives the addition product.



We will consider several types of additions to alkenes, using a wide variety of reagents: water, borane, hydrogen, carbenes, halogens, oxidizing agents, and even other alkenes. Most, but not all, of these will be electrophilic additions. Table 9-1 summarizes the classes of additions we will cover. Note that the table shows what elements have added across the double bond in the final product, but it says nothing about reagents or mechanisms. As we study these reactions, you should note the *regiochemistry* of each reaction, also called the *orientation of addition*, meaning which part of the reagent adds to which end of the double bond. Also note the *stereochemistry* if the reaction is stereospecific.

TABLE 9-1 Types of Additions to Alkenes

$>C=C<$ $\xrightarrow[\text{[Elements Added]}^a]{\text{Type of Addition}}$ Product

Type of Addition [Elements Added]	Product	Type of Addition [Elements Added]	Product
(水合反应) hydration [H_2O]		(加卤素反应) halogenation [X_2], an oxidation	
(加氢反应) hydrogenation [H_2], a reduction		(加次卤酸反应) halohydrin formation [HOX], an oxidation	
(羟基化反应) hydroxylation [HOOH], an oxidation		(加卤化氢反应) HX addition [HX]	
(氧化断裂反应) oxidative cleavage [O_2], an oxidation		(环丙烷化反应) cyclopropanation [CH_2]	
(环氧化反应) epoxidation [O], an oxidation			

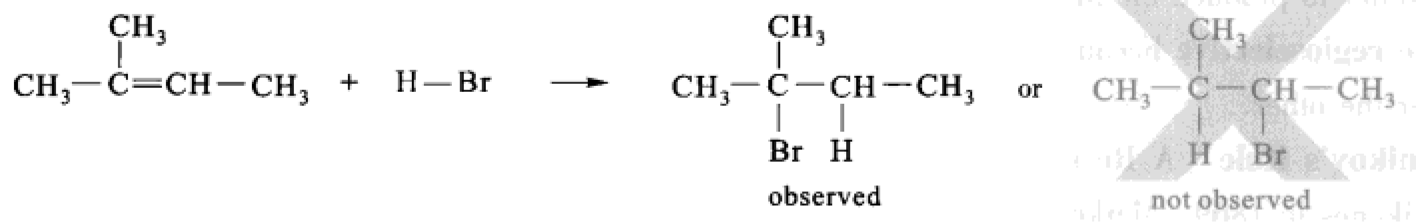
[a] These are not the reagents used but simply the groups that appear in the product.

9-3 Addition of Hydrogen Halides to Alkenes

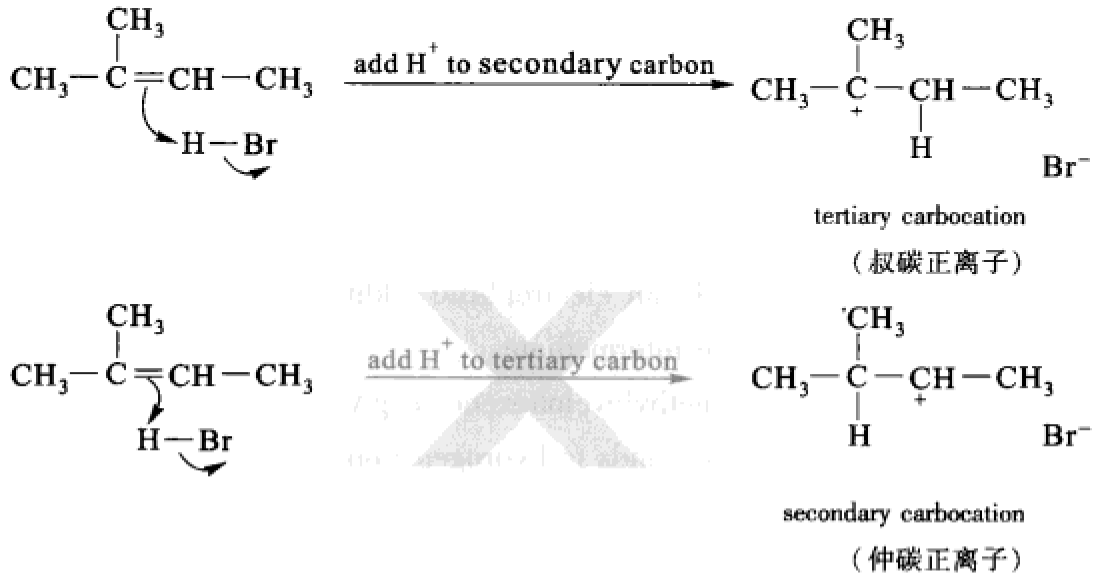
9-3A Orientation of Addition: Markovnikov's Rule

The simple mechanism shown for addition of HBr to 2-butene applies to a large number of electrophilic additions. We can use this mechanism to predict the outcome of some fairly complicated reactions. For example, the addi-

tion of HBr to 2-methyl-2-butene could lead to either of two products, yet only one is observed.

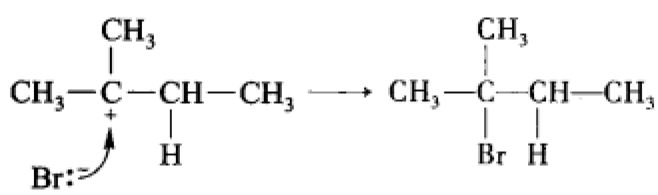


The first step is protonation of the double bond. If the proton adds to the secondary carbon, the product will be different from the one formed if the proton adds to the tertiary carbon.



When the proton adds to the secondary carbon, a tertiary carbocation results. When the proton adds to the tertiary carbon atom, a secondary carbocation results. The tertiary carbocation is more stable (see Section 5-16), so the first reaction is favored.

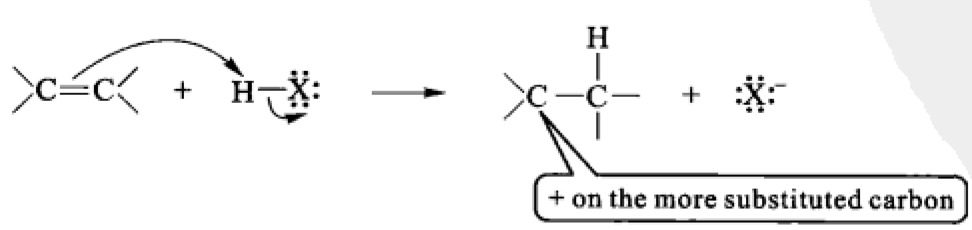
The second half of the mechanism produces the final product of the addition of HBr to 2-methyl-2-butene.



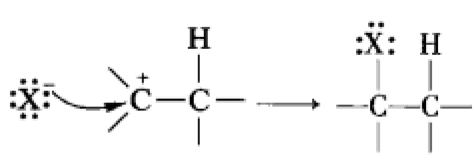
Note that protonation of one carbon atom of a double bond gives a carbocation on the carbon atom that was *not* protonated. Therefore, the proton adds to the end of the double bond that is *less* substituted to give the *more substituted carbocation* (the more stable carbocation).

MECHANISM 9-2 Ionic Addition of HX to an Alkene

Step 1: Protonation of the pi bond forms a carbocation.



Step 2: Attack by the halide ion gives the addition product.



There are many examples of reactions where the proton adds to the less substituted carbon atom of the double bond in order to produce the more substituted carbocation. The addition of HBr (and other hydrogen halides) is said to be **regioselective** because in each case, one of the two possible orientations of addition results preferentially over the other.

Markovnikov's Rule A Russian chemist, Vladimir Markovnikov, first showed the orientation of addition of HBr to alkenes in 1869. Markovnikov stated:

MARKOVNIKOV'S RULE: The addition of a proton acid to the double bond of an alkene results in a product with the acid proton bonded to the carbon atom that already holds the greater number of hydrogen atoms.

This is the original statement of **Markovnikov's rule**. Reactions that follow this rule are said to follow **Markovnikov orientation** and give the **Markovnikov product**. We are often interested in adding electrophiles other than proton acids to the double bonds of alkenes. Markovnikov's rule can be extended to include a wide variety of other additions, based on the addition of the electrophile in such a way as to produce the most stable carbocation.

MARKOVNIKOV'S RULE (extended): In an electrophilic addition to an alkene, the electrophile adds in such a way as to generate the most stable intermediate.

Figure 9−2 shows how HBr adds to 1-methylcyclohexene to give the product with an additional hydrogen bonded to the carbon that already had the most bonds to hydrogen (one) in the alkene. Note that this orientation results from addition of the proton in the way that generates the more stable carbocation.

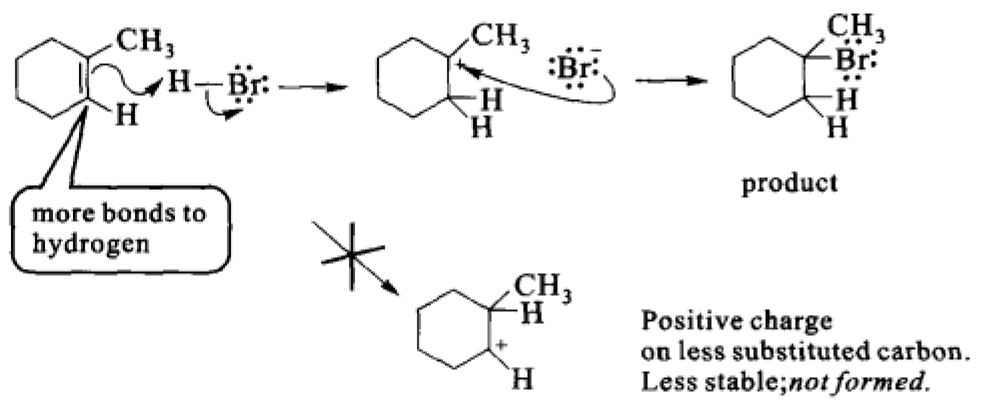
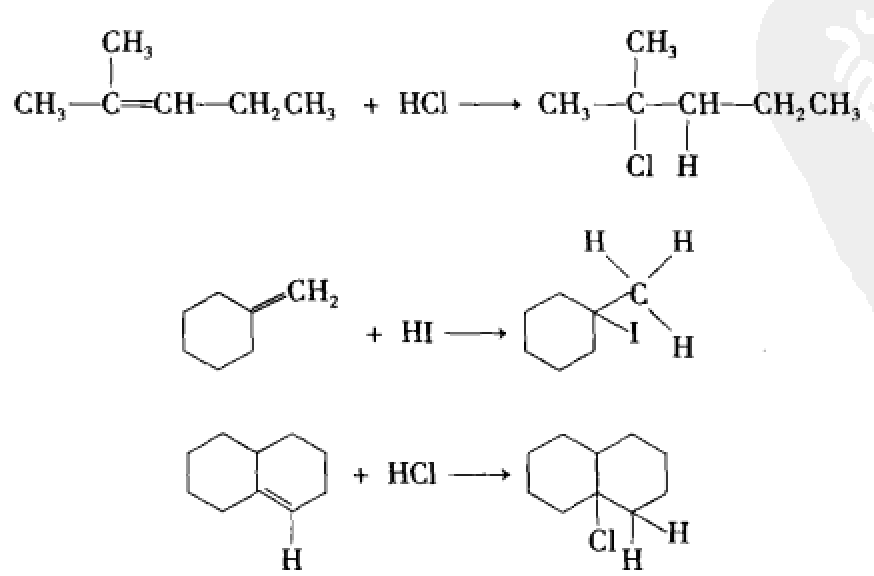


Figure 9−2 An electrophile adds to the less substituted end of the double bond to give the more substituted (and therefore more stable) carbocation.

Like HBr, both HCl and HI add to the double bonds of alkenes, and they also follow Markovnikov's rule; for example,



PROBLEM 9−1

When 1,3-butadiene reacts with 1 mol of HBr, both 3-bromo-1-butene and 1-bromo-2-butene are formed. Propose a mechanism to account for this mixture of products.

9−3B Free-Radical Addition of HBr: Anti-Markovnikov Addition

In 1933, M. S. Kharasch and F. W. Mayo showed that **anti-Markovnikov products** result from addition of HBr (but not HCl of HI) in the presence of peroxides. Peroxides give rise to free radicals that act as catalysts to accelerate the addition, causing it to occur by a different mechanism. The oxygen-oxygen bond in peroxides is rather weak. It can break to give two radicals.

$$R{-}\ddot{\underset{..}{O}}{-}\ddot{\underset{..}{O}}{-}R \xrightarrow{\text{heat}} R{-}\ddot{\underset{..}{O}}\cdot \; + \; \cdot\ddot{\underset{..}{O}}{-}R \qquad \Delta H^{\ominus} = +150 \text{ kJ/mol}$$

Alkoxy radicals (R—O·) catalyze the anti-Markovnikov addition of HBr. The mechanism of this free-radical chain reaction is shown next.

MECHANISM 9−3 Free-Radical Addition of HBr to Alkenes

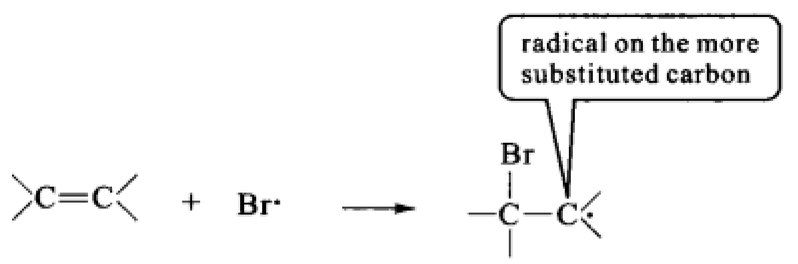
Initiation: Radicals are formed.

$$R{-}O{-}O{-}R \xrightarrow{\text{heat}} R{-}O\cdot \; + \; \cdot O{-}R$$

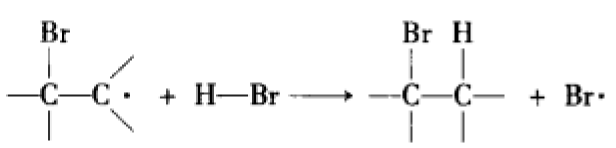
$$R{-}O\cdot \; + \; H{-}Br \longrightarrow R{-}O{-}H \; + \; Br\cdot$$

Propagation: A radical reacts to generate another radical.

Step 1: A bromine radical adds to the double bond to generate an alkyl radical on the more substituted carbon atom.



Step 2: The alkyl radical abstracts a hydrogen atom from HBr to generate the product and a bromine radical.

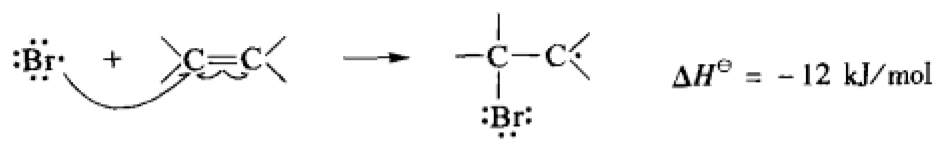


The bromine radical generated in Step 2 goes on to react in Step 1, continuing the chain.

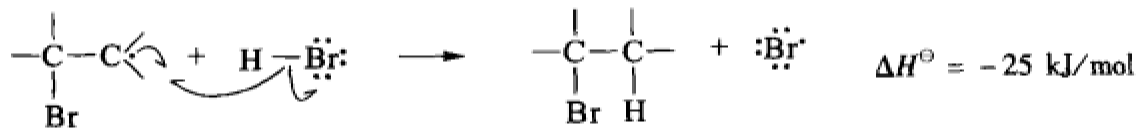
Let's consider the individual steps. In the initiation step, free radicals generated from the peroxide react with HBr to form bromine radicals.

$$R{-}\ddot{\underset{..}{O}}\cdot \; + \; H{-}\ddot{\underset{..}{Br}}: \longrightarrow R{-}\ddot{\underset{..}{O}}{-}H \; + \; :\ddot{\underset{..}{Br}}\cdot \qquad \Delta H^{\ominus} = -63 \text{ kJ/mol}$$

The bromine radical lacks an octet of electrons in its valence shell, making it electrondeficient and electrophilic. It adds to a double bond, forming a new free radical with the odd electron on a carbon atom.

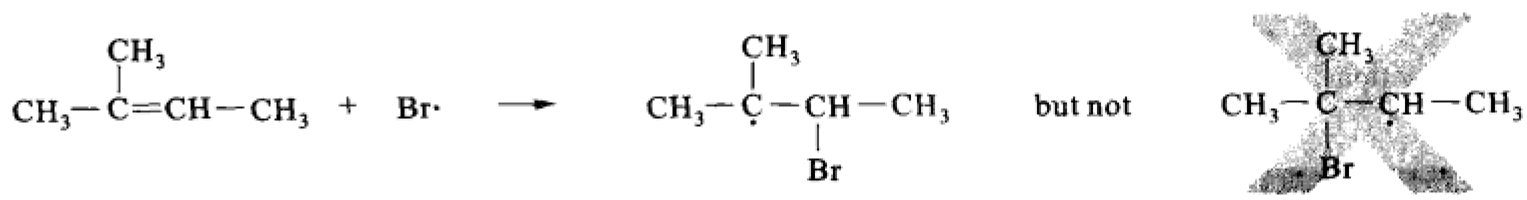


This free radical reacts with an HBr molecule to form a C—H bond and generate another bromine radical.



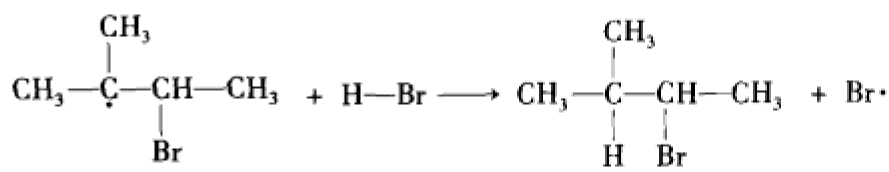
The regenerated bromine radical reacts with another molecule of the alkene, continuing the chain reaction. Note that each propagation step starts with one free radical and ends with another free radical. The number of free radicals is constant, until free radicals come together and terminate the chain reaction.

Radical Addition of HBr to Unsymmetrical Alkenes Now we must explain the anti-Markovnikov orientation found in the products of the peroxide-catalyzed reaction. When the alkene is unsymmetrical, adding the bromine radical to the secondary end of the double bond forms a tertiary radical.



tertiary radical (more stable) (叔碳自由基) — secondary radical (less stable) (仲碳自由基)

As we saw in the protonation of an alkene, the electrophile (in this case, Br·) adds to the less substituted end of the double bond, and the unpaired electron appears on the more substituted carbon to give the more stable free radical. This intermediate reacts with HBr to give the anti-Markovnikov product, in which H has added to the more substituted end of the double bond: the end that started with *fewer* hydrogens.

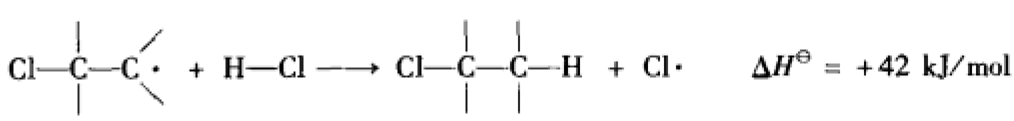


anti-Markovnikov product
(反马氏产物)

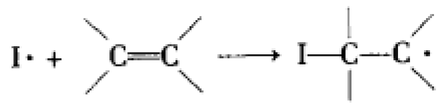
Note that *both* mechanisms for the addition of HBr to an alkene (with and without peroxides) follow our extended statement of Markovnikov's rule: In both cases, the electrophile adds to the less substituted end of the double bond to give the more stable carbocation or free radical. In the ionic reaction, the electrophile is H^+. In the peroxide-catalyzed free-radical reaction, Br· is the electrophile.

Many students wonder why the reaction with Markovnikov orientation does not take place in the presence of peroxides, together with the free-radical chain reaction. It actually does take place, but the peroxide-catalyzed reaction is faster. If just a tiny bit of peroxide is present, a mixture of Markovnikov and anti-Markovnikov products results. If an appreciable amount of peroxide is present, the radical chain reaction is so much faster than the uncatalyzed ionic reaction that only the anti-Markovnikov product is observed.

The reversal of orientation in the presence of peroxides is called the **peroxide effect**. It occurs only with the addition of HBr to alkenes. The reaction of an alkyl radical with HCl is strongly endothermic, so the free-radical chain reaction is not effective for the addition of HCl.



Similarly, the reaction of an iodine atom with an alkene is strongly endothermic, and the free-radical addition of HI is not observed. Only HBr has just the right reactivity for each step of the free-radical chain reaction to take place.



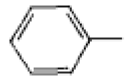
$\Delta H^{\ominus} = +54$ kJ/mol

PROBLEM 9-2

Predict the major products of the following reactions, and propose mechanisms to support your predictions.

(a) 2-methylpropene + HBr + $CH_3-\overset{\overset{O}{\|}}{C}-O-O-\overset{\overset{O}{\|}}{C}-CH_3$

(b) 1-methylcyclopentene + HBr + $CH_3CH_2-O-O-CH_2CH_3$

(c) 1-phenylpropene + HBr + di-*t*-butyl peroxide (二叔丁基过氧化物) (phenyl = Ph = )

PROBLEM 9-3

Show how you would accomplish the following synthetic conversions.

(a) Convert 1-methylcyclohexene to 1-bromo-1-methylcyclohexane

(b) Convert 1-methylcyclohexanol to 1-bromo-2-methylcyclohexane

PROBLEM 9-4

Show how you would accomplish the following synthetic conversions.

(a) 1-butene ⟶ 1-bromobutane

(b) 1-butene ⟶ 2-bromobutane

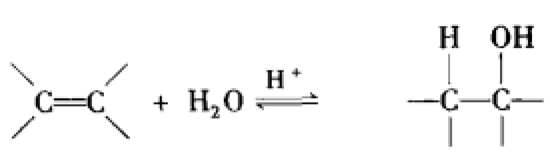
(c) 2-methylcyclohexanol ⟶ 1-bromo-1-methylcyclohexane

(d) 2-methyl-2-butanol ⟶ 2-bromo-3-methylbutane

9-4 Addition of Water: Hydration of Alkenes

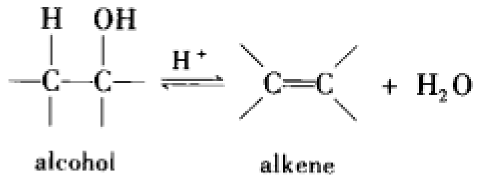
An alkene may react with water in the presence of a strongly acidic catalyst to form an alcohol. Formally, this reaction is a **hydration** (the addition of water), with a hydrogen atom adding to one carbon and a hydroxyl group adding to the other. Hydration of an alkene is the reverse of the dehydration of alcohols we studied in Section 8-8.

Hydration of an alkene



alkene — alcohol (Markovnikov orientation) (马氏定向)

Dehydration of an alcohol



For dehydrating alcohols, a concentrated dehydrating acid (such as H_2SO_4 or H_3PO_4) is used to drive the equilibrium to favor the alkene. Hydration of an alkene, on the other hand, is accomplished by adding excess water to drive the equilibrium toward the alcohol.

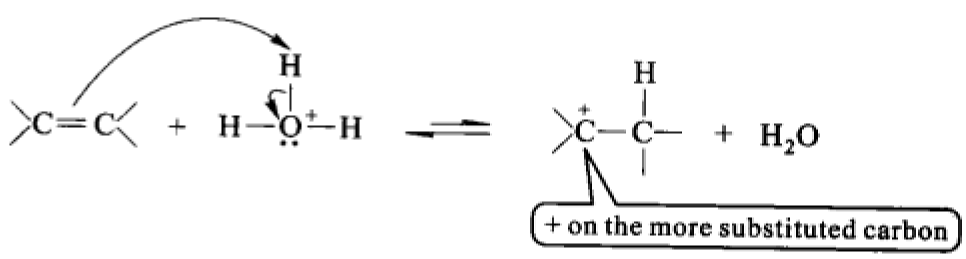
9-4A Mechanism of Hydration

The *principle of microscopic reversibility* states that a forward reaction and a reverse reaction taking place under the same conditions (as in an equilibrium) must follow the same reaction pathway in microscopic detail. The hydration and dehydration reactions are the two complementary reactions in an equilibrium; therefore, they must follow the same reaction pathway. It makes sense that the lowest-energy transition states and intermediates for the reverse reaction are the same sa those for the forward reaction, except in reverse order.

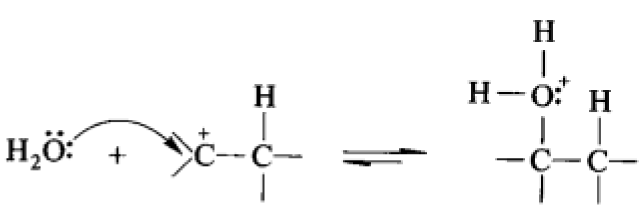
According to the principle of microscopic reversibility, we can write the hydration mechanism by reversing the order of the steps of the dehydration (Section 8-8). Protonation of the double bond forms a carbocation. Nucleophilic attack by water, followed by loss of a proton, gives the alcohol.

MECHANISM 9-4 Acid-Catalyzed Hydration of an Alkene

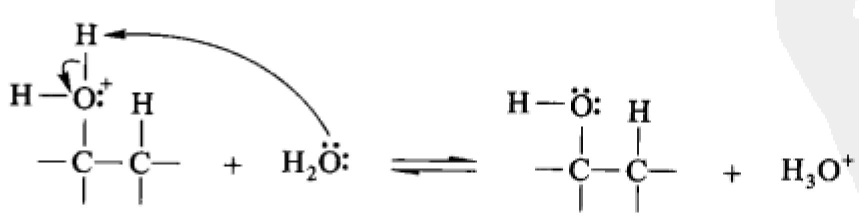
***Step 1*:** Protonation of the double bond forms a carbocation.



***Step 2*:** Nucleophilic attack by water gives a protonated alcohol.



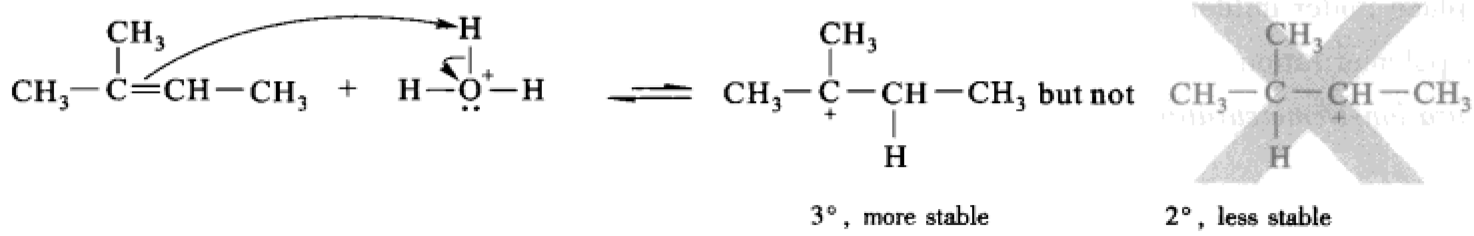
***Step 3*:** Deprotonation gives the alcohol.



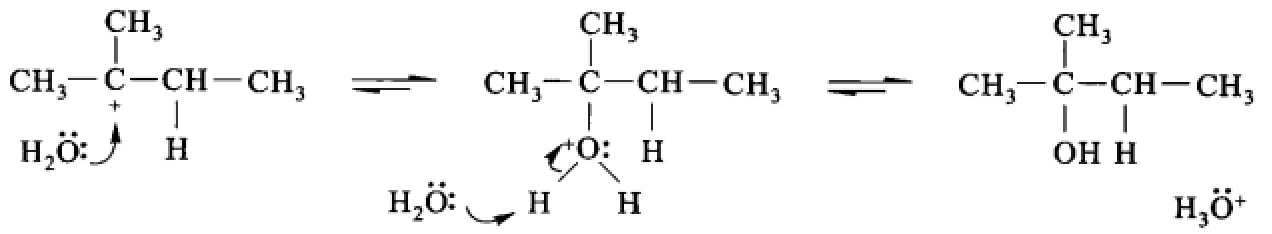
9-4B Orientation of Hydration

Step 1 of the hydration mechanism is similar to the first step in the addition of HBr. The proton adds to the *less* substituted end of the double bond to form the *more* substituted carbocation. Water attacks the carbocation to give (after loss of a proton) the alcohol with the —OH group on the more substituted carbon. Like the addition of

hydrogen halides, hydration is *regioselective*: It follows Markovnikov's rule, giving a product in which the new hydrogen has added to the less substituted end of the double bond. Consider the hydration of 2-methyl-2-butene:

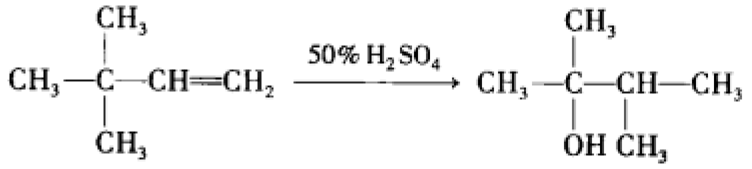


The proton adds to the less substituted end of the double bond, so the positive charge appears at the more substituted end. Water attacks the carbocation to give the protonated alcohol.



The reaction follows Markovnikov's rule. The proton has added to the end of the double bond that already had more hydrogens (that is, the less substituted end), and the —OH group has added to the more substituted end.

Like other reactions that involve carbocation intermediates, hydration may take place with rearrangement. For example, when 3,3-dimethyl-1-butene undergoes acidcatalyzed hydration, the major product results from rearrangement of the carbocation intermediate.



3,3-dimethyl-1-butene 2,3-dimethyl-2-butanol (major product)

PROBLEM 9-5

Propose a mechanism to show how 3,3-dimethyl-1-butene reacts with dilute aqueous H_2SO_4 to give 2,3-dimethyl-2-butanol and a small amount of 2,3-dimethyl-2-butene.

PROBLEM 9-6

Predict the products of the following hydration reactions.

(a) 1-methylcyclopentene + dilute acid

(b) 2-phenylpropene + dilute acid

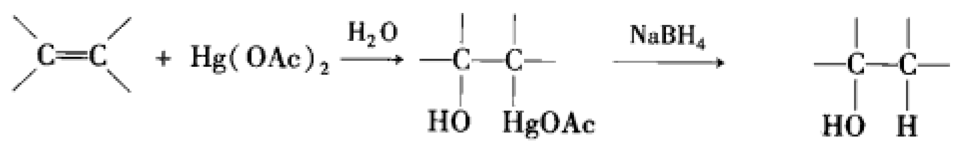
(c) 1-phenylcyclohexene + dilute acid

9-5 Hydration by Oxymercuration-Demercuration

Many alkenes do not easily undergo hydration in aqueous acid. Some alkenes are nearly insoluble in aqueous acid, and others undergo side reactions such as rearrangement, polymerization, or charring under these strongly acidic conditions. In some cases, the overall equilibrium favors the alkene rather than the alcohol. No amount of catalysis can cause a reaction to occur if the energetics are unfavorable.

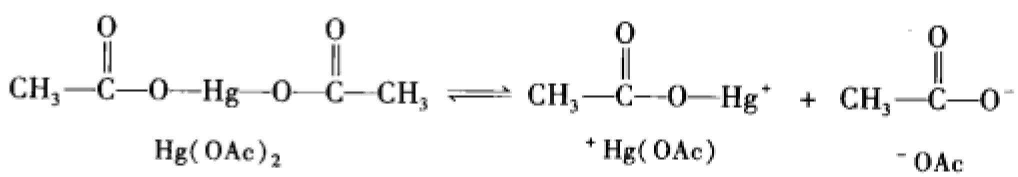
Oxymercuration-demercuration is another method for converting alkenes to alcohols with Markovnikov orientation. Oxymercuration-demercuration works with many alkenes that do not easily undergo direct hydration, and it takes place under milder conditions. No free carbocation is formed, so there is no opportunity for rearrangements or polymerization.

Oxymercuration-Demercuration



(Markovnikov orientation)

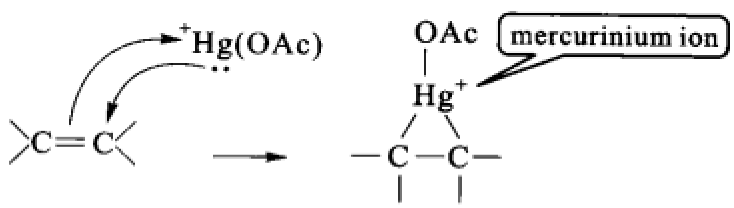
The reagent for mercuration is mercuric acetate, $Hg(OCOCH_3)_2$, abbreviated $Hg(OAc)_2$. There are several theories as to how this reagent acts as an electrophile; the simplest one is that mercuric acetate dissociates slightly to form a positively charged mercury species, $^+Hg(OAc)$.



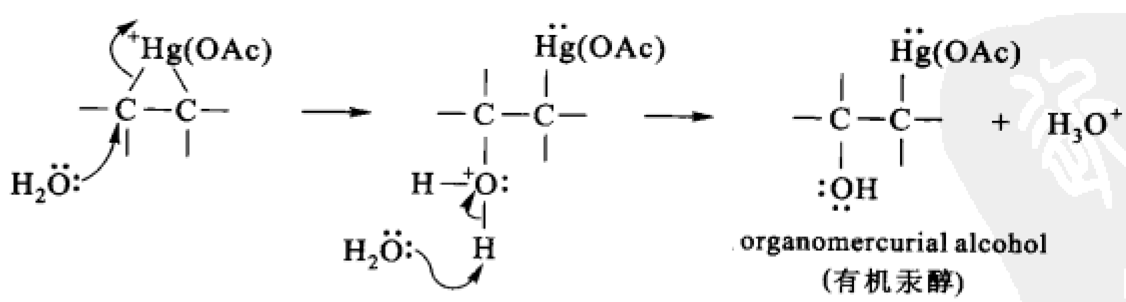
Oxymercuration involves an electrophilic attack on the double bond by the positively charged mercury species. The product is a *mercurinium ion*, an organometallic cation containing a three-membered ring. In the second step, water from the solvent attacks the mercurinium ion to give (after deprotonation) an organomercurial alcohol. A subsequent reaction is **demercuration**, to remove the mercury. Sodium borohydride ($NaBH_4$, a reducing agent) replaces the mercuric acetate fragment with a hydrogen atom.

MECHANISM 9-5 Oxymercuration of an Alkene

Step 1: Electrophilic attack forms a mercurinium ion.

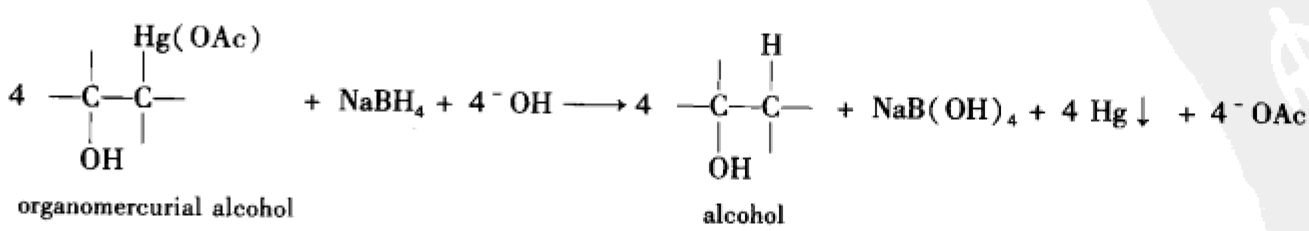


Step 2: Water opens the ring to give an organomercurial alcohol.



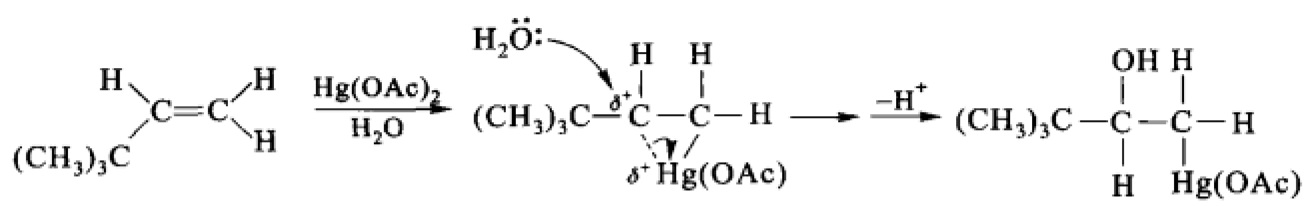
organomercurial alcohol
(有机汞醇)

Demercuration replaces the mercuric fragment with hydrogen to give the alcohol.

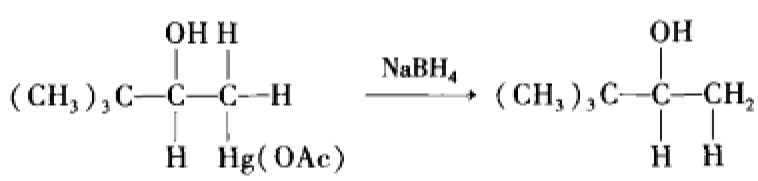


Oxymercuration-demercuration of an unsymmetrical alkene generally gives Markovnikov orientation of addition, as shown by the oxymercuration of propene in the preceding example. In this unsymmetrical case, the mercurinium ion has a considerable amount of positive charge on the more substituted carbon atom. Attack by water occurs on this more electrophilic carbon, giving Markovnikov orientation. The electrophile, $^{+}Hg(OAc)$, remains bonded to the less substituted end of the double bond. Reduction of the organomercurial alcohol gives the Markovnikov alcohol: 2-propanol.

Similarly, oxymercuration-demercuration of 3,3-dimethyl-1-butene gives the Markovnikov product, 3,3-dimethyl-2-butanol, in excellent yield. Contrast this unrearranged product with the rearranged product formed in the acid-catalyzed hydration of the same alkene in Section 9-4B. Oxymercuration-demercuration reliably adds water across the double bond of an alkene with Markovnikov orientation and without rearrangement.



3, 3-dimethyl-1-butene mercurinium ion Markovnikov product

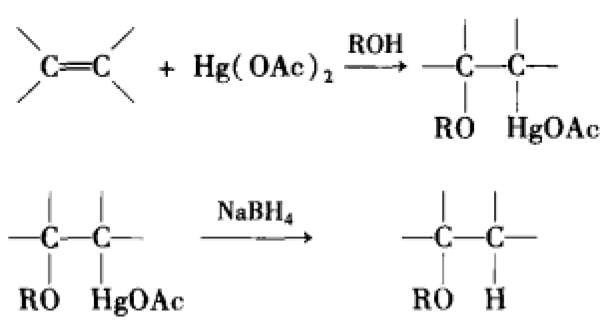


Markovnikov product (马氏产物) 3,3-dimethyl-2-butanol (94% overall)

Of the methods we have seen for Markovnikov hydration of alkenes, oxymercuration-demercuration is most commonly used in the laboratory. It gives better yields than direct acid-catalyzed hydration, it avoids the possibility of rearrangements, and it does not involve harsh conditions. There are also disadvantages, however. Organomercurial compounds are highly toxic. They must be used with great care and then must be disposed of properly.

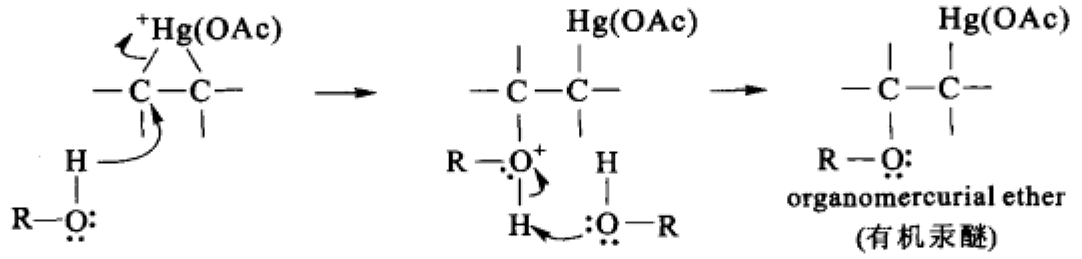
9-6 Alkoxymercuration-Demercuration

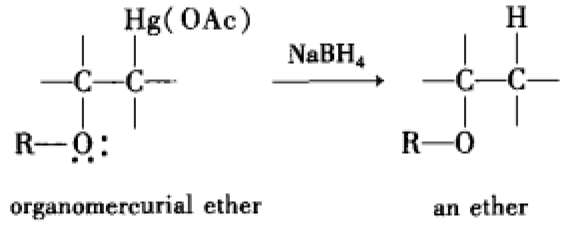
When mercuration takes place in an alcohol solvent, the alcohol serves as a nucleophile to attack the mercurinium ion. The resulting product contains an alkoxy (—O—R) group. In effect, **alkoxymercuration**-demercuration converts alkenes to ethers by adding an alcohol across the double bond of the alkene.



(Markovnikov orientation)

As we have seen, an alkene reacts to form a mercurinium ion that is attacked by the nucleophilic solvent. Attack by an alcohol solvent gives an organomercurial ether that can be reduced to the ether.





The solvent attacks the mercurinium ion at the *more* substituted end of the double bond (where there is more δ^+ charge), giving Markovnikov orientation of addition. The Hg(OAc) group appears at the *less* substituted end of the double bond. Reduction gives the Markovnikov product, with hydrogen at the less substituted end of the double bond.

PROBLEM 9-7

Show the intermediates and products that result from alkoxymercuration-demercuration of 1-methylcyclopentene, using methanol sa the solvent.

PROBLEM 9-8

Predict the major products of the following reactions.

(a) 1-methylcyclohexene + aqueous $Hg(OAc)_2$

(b) the product from part (a), treated with $NaBH_4$

(c) 4-chlorocycloheptene + $Hg(OAc)_2$ in CH_3OH

(d) the product from part (c), treated with $NaBH_4$

PROBLEM 9-9

Show how you would accomplish the following synthetic conversions.

(a) 1-butene → 2-methoxybutane

(b) 1-iodo-2-methylcyclopentane → 1-methylcyclopentanol

(c) 3-methyl-1-pentene → 3-methyl-2-pentanol

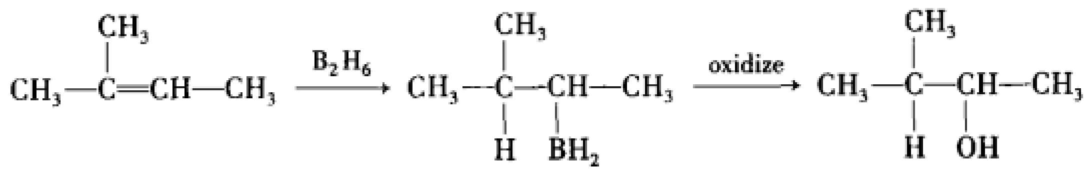
Explain why acid-catalyzed hydration would be a poor choice for the reaction in (c).

9-7 Hydroboration of Alkenes

We have seen two methods for hydrating an alkene with Markovnikov orientation. What if we need to convert an alkene to the anti-Markovnikov alcohol? For example, the following transformation cannot be accmplished using the hydration procedures covered thus far.

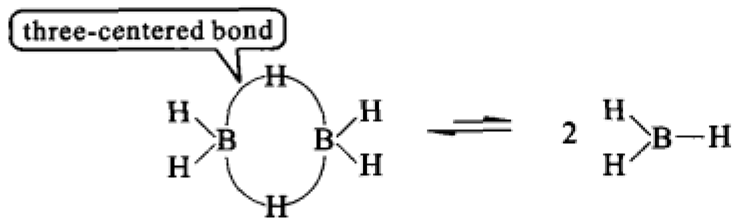
Such an anti-Markovnikov hydration was impossible until H. C. Brown, of Purdue University, discovered that dib-

orane (B_2H_6) adds to alkenes with anti-Markovnikov orientation to form alkylboranes, which can be oxidized to give anti-Markovnikov alcohols. This discovery led to the development of a large field of borane chemistry, for which Brown received the Nobel Prize in chemistry in 1979.



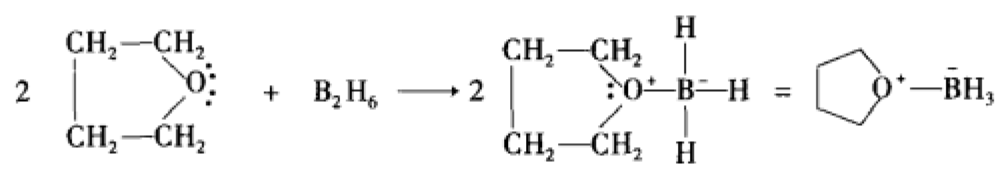
2-methyl-2-butene — an alkylborane (烷基硼烷) — 3-methyl-2-butanol (>90%)

Diborane (B_2H_6) is a dimer composed of two molecules of borane (BH_3). The bonding in diborane is unconventional, using three-centered (banana-shaped) bonds with protons in the middle of them. Diborane is in equilibrium with a small amount of borane (BH_3), a strong Lewis acid with only six valence electrons.



diborane (乙硼烷) — borane (甲硼烷)

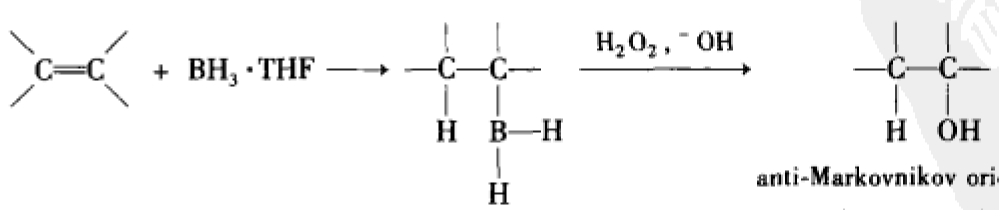
Diborane is an inconvenient reagent. It is a toxic, flammable, and explosive gas. It is more easily used as a complex with tetrahydrofuran (THF), a cyclic ether. This complex reacts like diborane, yet the solution is easily measured and transferred.



tetrahydrofuran (THF, 四氢呋喃) — diborane — borane-THF complex — $= BH_3 \cdot THF$

The $BH_3 \cdot THF$ reagent is the form of borane commonly used in organic reactions. BH_3 adds to the double bond of an alkene to give an alkylborane. Basic hydrogen peroxide oxidizes the alkylborane to an alcohol. In effect, hydroboration-oxidation converts alkenes to alcohols by adding water across the double bond, with anti-Markovnikov orientation.

Hydroboration-oxidation



anti-Markovnikov orientation
(syn stereochemistry)

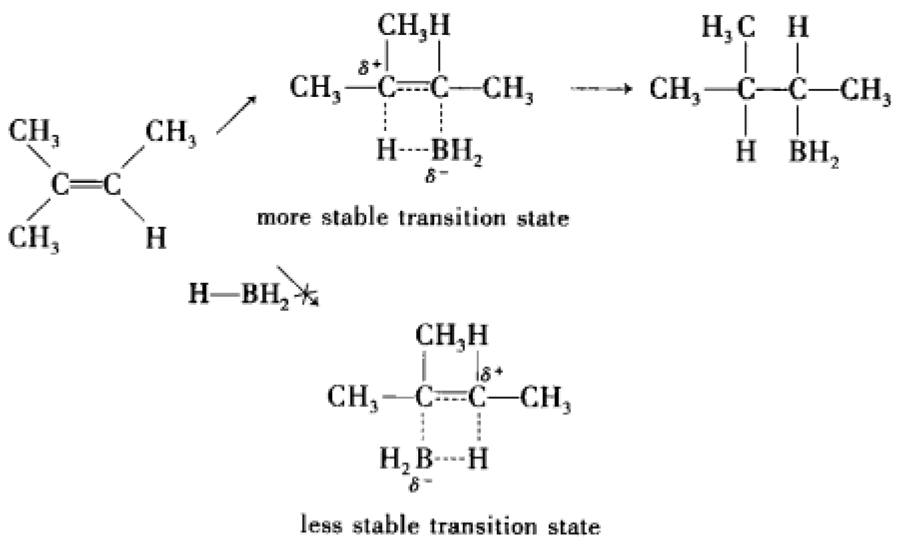
9-7A Mechanism of Hydroboration

Borane is an electron-deficient compound. It has only six valence electrons, so the boron atom cannot have an octet. Acquiring an octet is the driving force for the unusual bonding structures ("banana" bonds, for example) found in boron compounds. As an electron-deficient compound, BH_3 is a strong electrophile, capable of adding to a double bond. This **hydroboration** of the double bond is thought to occur in one step, with the boron atom adding to the less substituted end of the double bond, as shown in Mechanism 9-6.

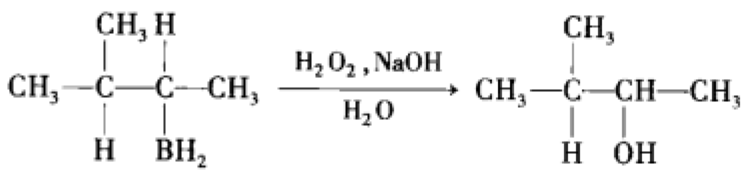
In the transition state, the electrophilic boron atom withdraws electrons from the pi bond, and the carbon at the other end of the double bond acquires a partial positive charge. This partial charge is more stable on the more substituted carbon atom. The product shows boron bonded to the less substituted end of the double bond and hydrogen bonded to the more substituted end. Also, steric hindrance favors boron adding to the less hindered, less substituted end of the double bond.

MECHANISM 9-6 Hydroboration of an Alkene

Borane adds to the double bond in a single step. Boron adds to the less hindered, less substituted carbon, and hydrogen adds to the more substituted carbon.



The boron atom is removed by oxidation, using aqueous sodium hydroxide and hydrogen peroxide (HOOH or H_2O_2) to replace the boron atom with a hydroxyl (—OH) group.



This hydration of an alkene by hydroboration-oxidation is another example of a reaction that does not follow the original statement of Markovnikov's rule (the product is anti-Markovnikov), but still follows our understanding of the reasoning behind Markovnikov's rule. The electrophilic boron atom adds to the *less* substituted end of the double bond, placing the positive charge (and the hydrogen atom) at the more substituted end.

PROBLEM 9-10

Show how you would convert 1-methylcyclopentanol to 2-methylcyclopentanol.

PROBLEM 9-11

Show how you would accomplish the following synthetic conversions.

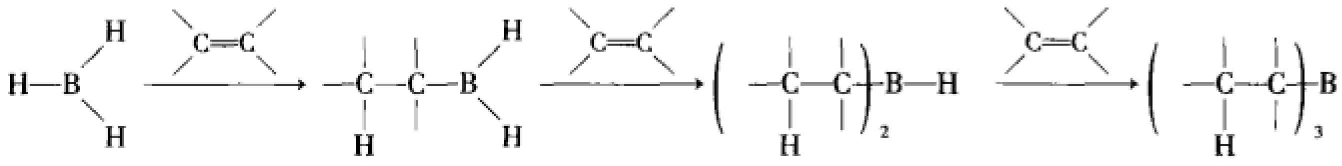
(a) 1-butene → 1-butanol (b) 1-butene → 2-butanol

(c) 2-bromo-2,4-dimethylpentane → 2,4-dimethyl-3-pentanol

9-7B Stoichiometry of Hydroboration

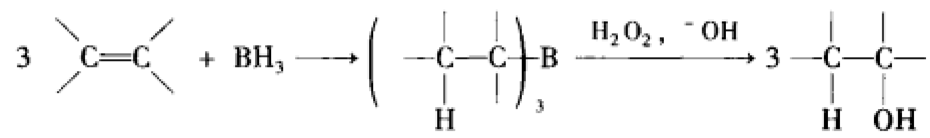
For simplicity, we have neglected the fact that 3 moles of an alkene react with each mole of BH_3. Each B—H

bond in BH_3 can add across the double bond of an alkene. The first addition forms an alkylborane, the second a dialkylborane, and the third a trialkylborane.



alkylborane dialkylborane trialkylborane

Summary

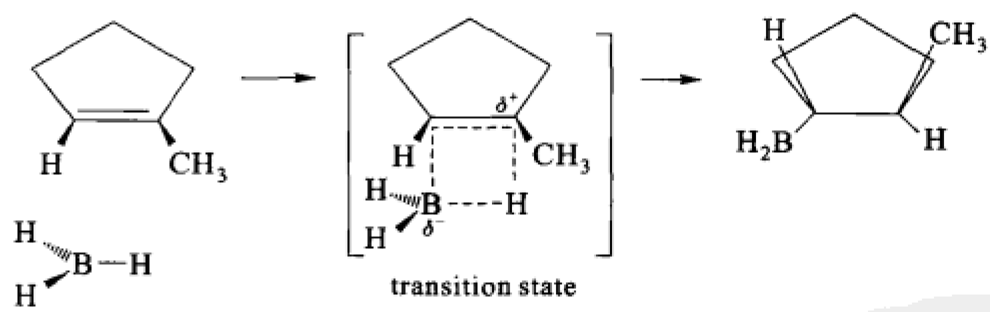


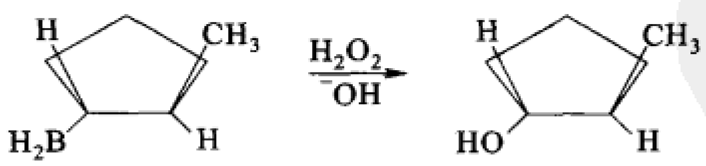
Trialkylboranes react exactly as we have discussed, and they oxidize to give anti-Markovnikov alcohols. Trialkylboranes are quite bulky, further reinforcing the preference for boron to add to the less hindered carbon atom of the double bond. Boranes are often drawn as the 1 : 1 monoalkylboranes to simplify their structure and emphasize the organic part of the molecule.

9-7C Stereochemistry of Hydroboration

The simultaneous addition of boron and hydrogen to the double bond (as shown in Mechanism 9-6) leads to a *syn addition*: Boron and hydrogen add across the double bond on the *same side* of the molecule. (If they added to opposite sides of the molecule, the process would be an *anti addition*.)

The stereochemistry of the hydroboration-oxidation of 1-methylcyclopentene is shown next. Boron and hydrogen add to the same face of the double bond (syn) to form a trialkylborane. Oxidation of the trialkylborane replaces boron with a hydroxyl group in the same stereochemical position. The product is *trans*-2-methylcyclopentanol. A racemic mixture is expected because a chiral product is formed from achiral reagents.

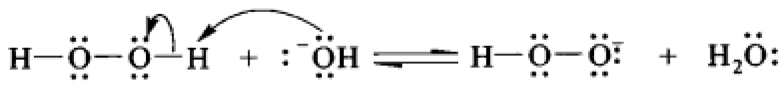




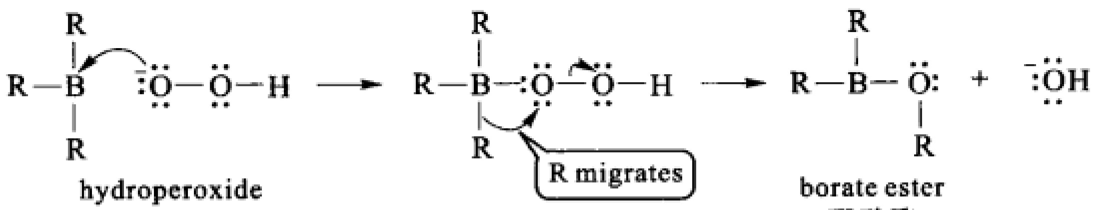
trans-2-methylcyclopentanol
(85% overall)
(racemic mixture of enantiomers)
(对映体外消旋混合物)

The second step (oxidation of the borane to the alcohol) takes place with retention of configuration. Hydroperoxide ion adds to the borane, causing the alkyl group to migrate from boron to oxygen. The alkyl group migrates with retention of configuration because it moves with its electron pair and does not alter the tetrahedral structure of the migrating carbon atom. Hydrolysis of the borate ester gives the alcohol.

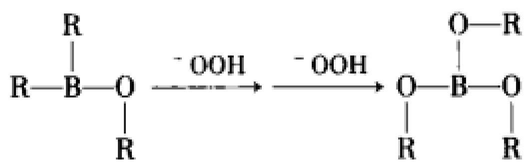
Formation of hydroperoxide ion



Addition of hydroperoxide and migration of the alkyl group

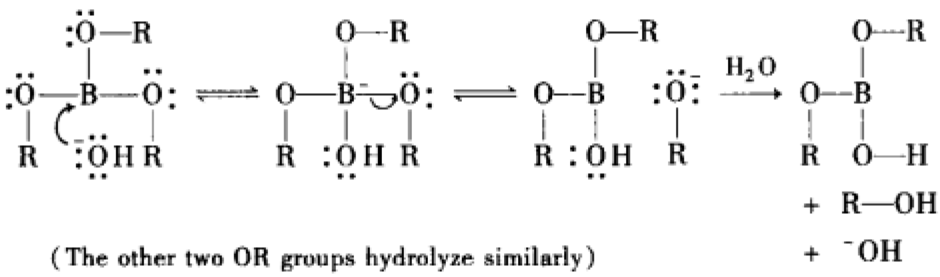


Twice more to oxidize the other two alkyl groups



trialkyl borate ester (硼酸三烷基酯)

Hydrolysis of the borate ester

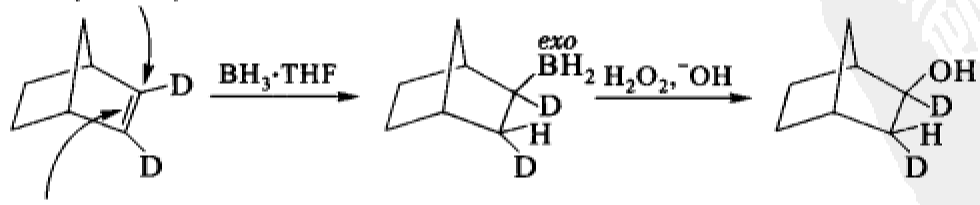


(The other two OR groups hydrolyze similarly)

Hydroboration of alkenes is another example of a **stereospecific reaction**, in which different stereoisomers of the starting compound react to give different stereoisomers of the product. Problem 9−12 considers the different products formed by the hydroboration-oxidation of two acyclic diastereomers.

SOLVED PROBLEM 9−1

A norbornene molecule labeled with deuterium is subjected to hydroboration-oxidation. Give the structures of the intermediates and products.



SOLUTION

The syn addition of BH_3 across the double bond of norbornene takes place mostly from the more accessible outside (exo) face of the double bond. Oxidation gives a product with both the hydrogen atom and the hydroxyl group in exo positions. (The less accessible inner face of the double bond is called the endo face.)

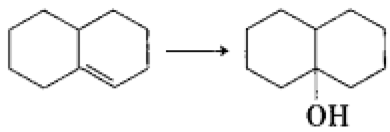
PROBLEM 9–12

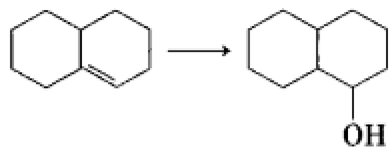
(**a**) When (*Z*)-3-methyl-3-hexene undergoes hydroboration-oxidation, two isomeric products are formed. Give their structures, and label each asymmetric carbon atom as (*R*) or (*S*). What is the relationship between these isomers?

(**b**) Repeat part (a) for (*E*)-3-methyl-3-hexene. What is the relationship between the products formed from (*Z*)-3-methyl-3-hexene and those formed from (*E*)-3-methyl-3-hexene?

PROBLEM 9–13

Show how you would accomplish the following transformations.

(**a**) 

(**b**) 

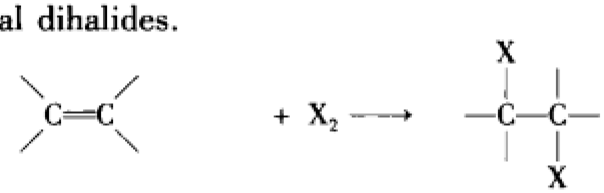
(**c**) 1-methylcycloheptanol → 2-methylcycloheptanol (2-甲基环庚醇)

PROBLEM 9–14

When HBr adds across the double bond of 1,2-dimethylcyclopentene, the product is a mixture of the cis and trans isomers. Show why this addition is not stereospecific.

9–8 Addition of Halogens to Alkenes

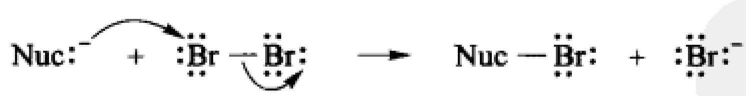
Halogens add to alkenes to form vicinal dihalides.



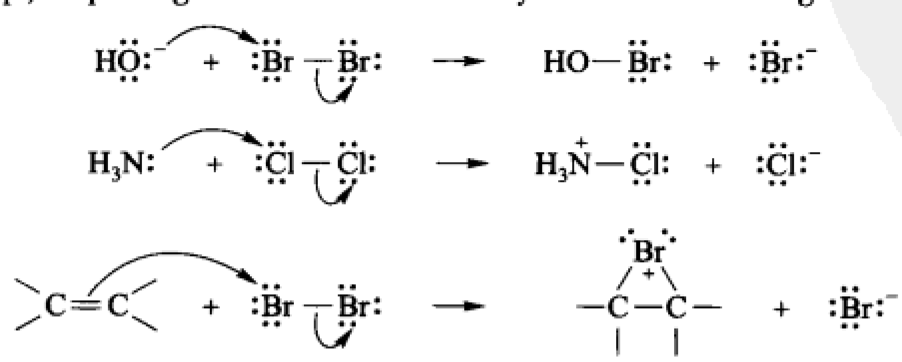
($X_2 = Cl_2$, Br_2, sometimes I_2) usually anti addition

9–8A Mechanism of Halogen Addition

A halogen molecule (Br_2, Cl_2, or I_2) is electrophilic; a nucleophile can react with a halogen, displacing a halide ion:



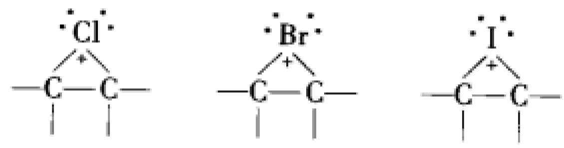
In this example, the nucleophile attacks the electrophilic nucleus of one bromine atom, and the other bromine serves as the leaving group, departing as bromide ion. Many reactions fit this general pattern; for example:



bromonium ion (溴鎓离子)

In the last reaction, the pi electrons of an alkene attack the bromine molecule, expelling bromide ion. A **bromonium ion** results, containing a three-membered ring with a positive charge on the bromine atom. This bromonium ion is similar in structure to the mercurinium ion discussed in Section 9-5. Similar reactions with other halogens form other **halonium ions**. The structures of a **chloronium ion**, a **bromonium ion**, and an **iodonium ion** are shown next.

Examples

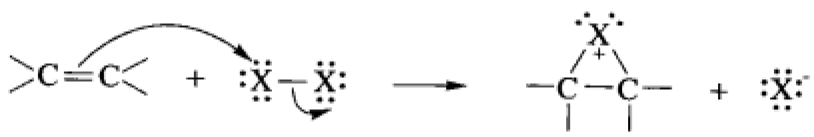


chloronium ion (氯鎓离子)　bromonium ion (溴鎓离子)　iodonium ion (碘鎓离子)

Unlike a normal carbocation, all the atoms in a halonium ion have filled octets. The three-membered ring has considerable ring strain, however, which, combined with a positive charge on an electronegative halogen atom, makes the halonium ion strongly electrophilic. Attack by a nucleophile, such as a halide ion, opens the halonium ion to give a stable product.

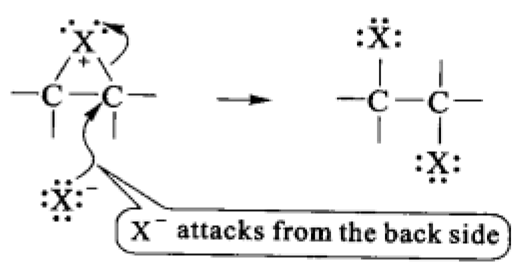
MECHANISM 9-7 Addition of Halogens to Alkenes

Step 1: Electrophilic attack forms a halonium ion.



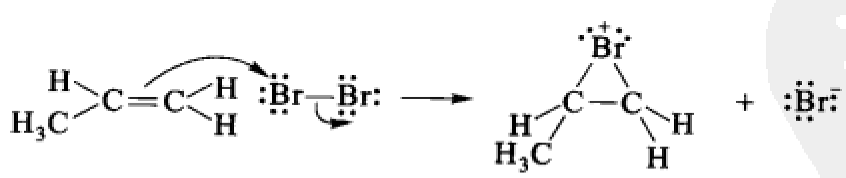
halonium ion (卤素鎓离子)

Step 2: The halide ion opens the halonium ion.



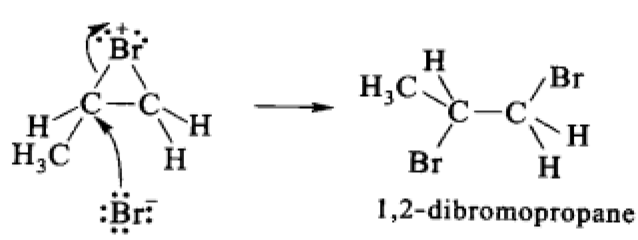
Example: **Addition of Br_2 to propene.**

Step 1: Electrophilic attack forms a bromonium ion.



propene　bromonium ion

Step 2: Bromide ion opens the bromonium ion.



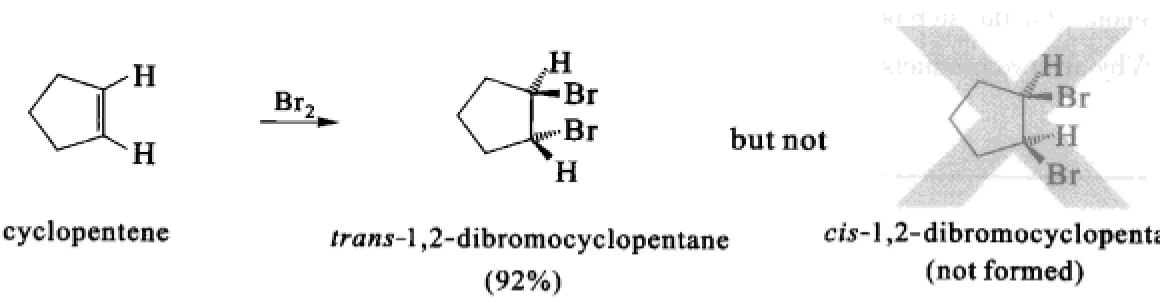
1,2-dibromopropane

Chlorine and bromine commonly add to alkenes by the halonium ion mechanism. Iodination is used less frequently because diiodide products decompose easily. Any solvents used must be inert to the halogens; methylene

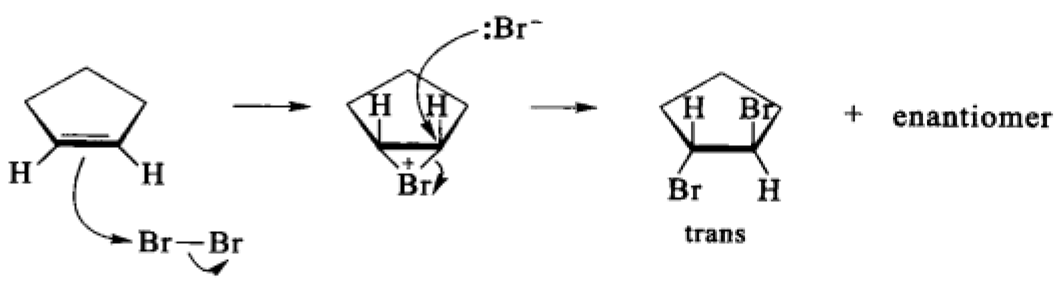
chloride (CH_2Cl_2), chloroform ($CHCl_3$), and carbon tetrachloride (CCl_4) are the most frequent choices.

9-8B Stereochemistry of Halogen Addition

The addition of bromine to cyclopentene is a stereospecific **anti addition**.



Anti stereochemistry results from the bromonium ion mechanism. When a nucleophile attacks a halonium ion, it must do so from the back side, in a manner similar to the S_N2 displacement. This back-side attack assures anti stereochemistry of addition.



Halogen addition is another example of a stereospecific reaction, in which different stereoisomers of the starting material give different stereoisomers of the product. Figure 9-3 shows additional examples of the anti addition of halogens to alkenes.

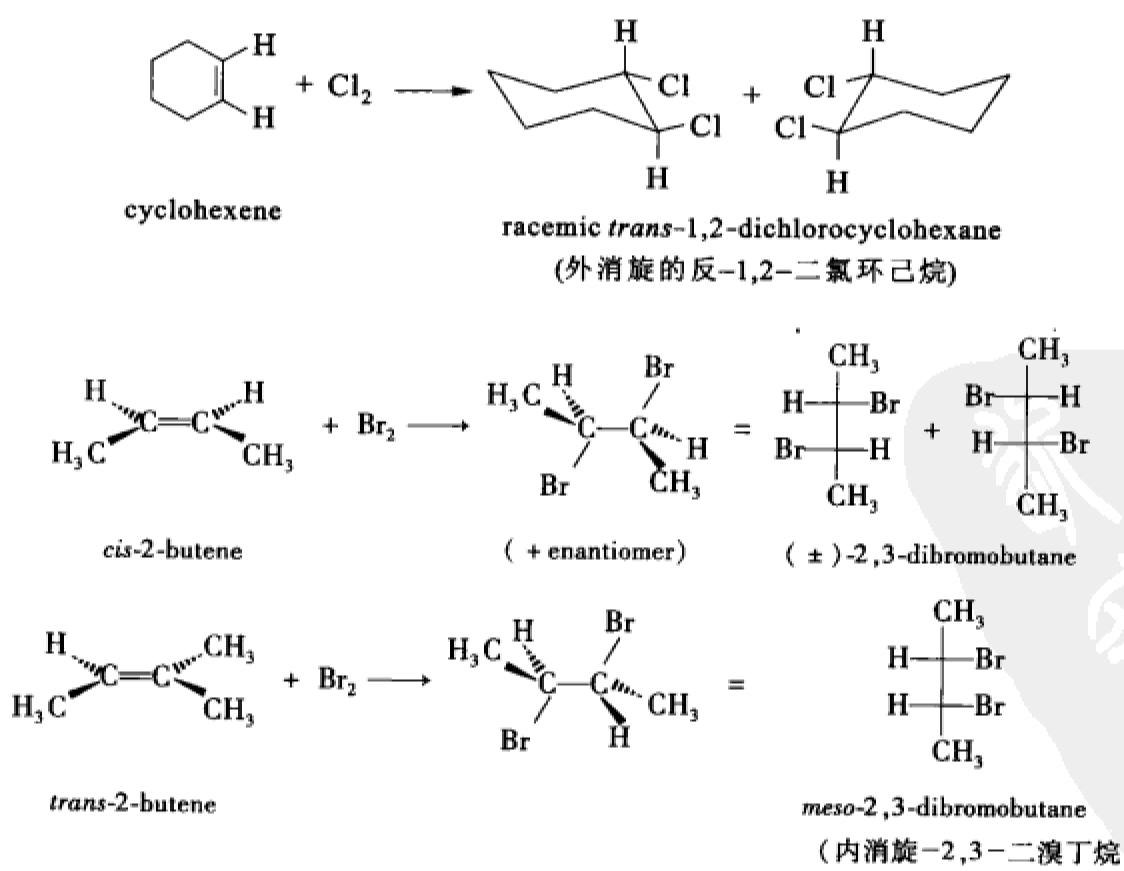


Figure 9-3 Examples of the anti addition of halogens to alkenes. The stereospecific anti addition gives predictable stereoisomers of the products.

The addition of bromine has been used as a simple chemical test for the presence of olefinic double bonds. A solution of bromine in carbon tetrachloride is a clear, deep red color. When this red solution is added to an

alkene, the red bromine color disappears (we say it is "decolorized"), and the solution becomes clear and colorless. (Although there are other functional groups that decolorize bromine, few do it as quickly as alkenes.)

PROBLEM 9-15

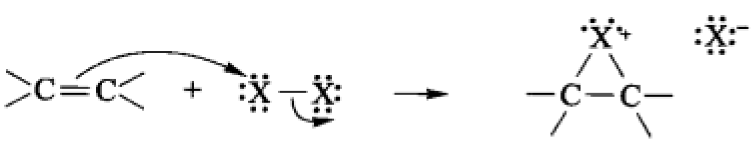
Give mechanisms to account for the stereochemistry of the products observed from the addition of bromine to *cis*-and *trans*-2-butene (Figure 9-3). Why are two products formed from the cis isomer but only one from the trans? (Making models will be helpful.)

9-9 Formation of Halohydrins

A **halohydrin** is an alcohol with a halogen on the adjacent carbon atom. In the presence of water, halogens add to alkenes to form halohydrins. The halogen adds to the alkene to give a halonium ion, which is strongly electrophilic. Water acts as a nucleophile to open the halonium ion and form the halohydrin.

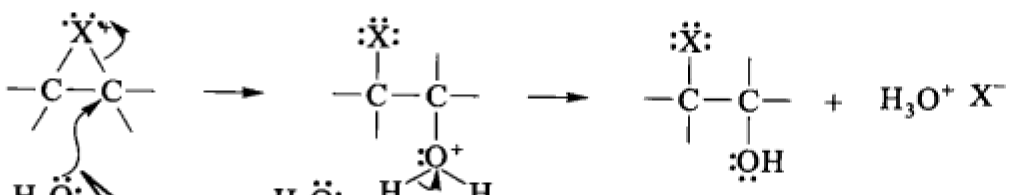
MECHANISM 9-8 Formation of Halohydrins

Step 1: Electrophilic attack forms a halonium ion.



(X=Cl,Br,or I) halonium ion

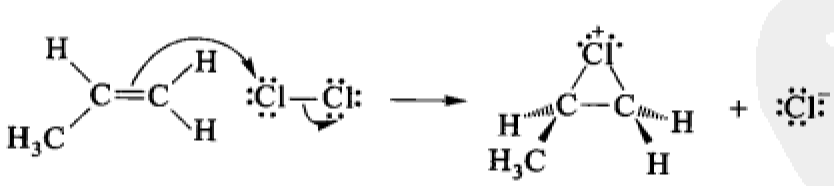
Step 2: Water opens the halonium ion; deprotonation gives the halohydrin.



halohydrin(卤代醇)
Markovnikov orientation
anti stereochemistry

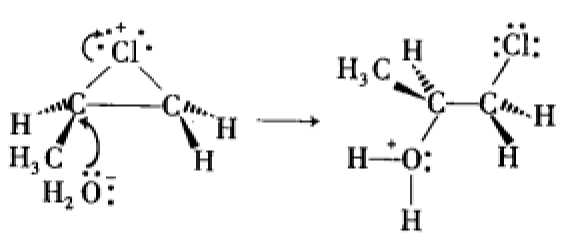
Example: **Addition of Cl_2 to propene in water.**

Step 1: Electrophilic attack forms a chloronium ion.

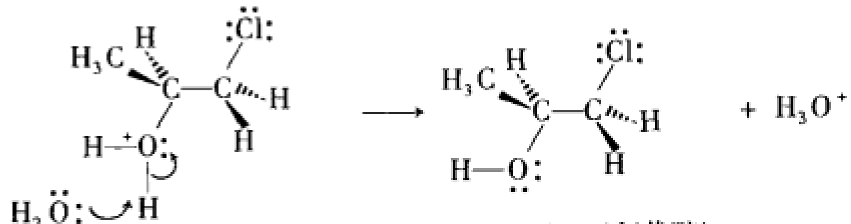


propene chloronium ion

Step 2: Back-side attack by water opens the chloronium ion.

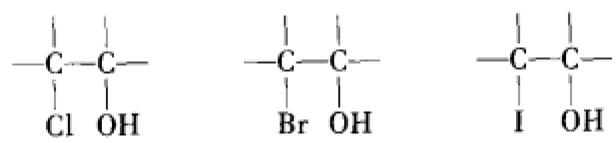


Step 3: Water removes a proton to give the chlorohydrin.



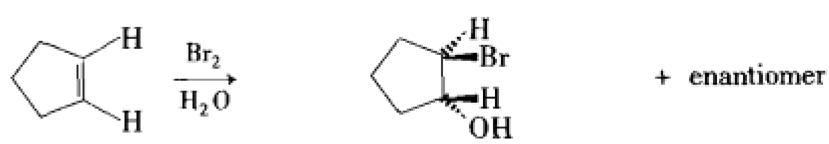
chlorohydrin（氯代醇）

When halogenation takes place with no solvent or with an inert solvent such as carbon tetrachloride (CCl_4) or chloroform ($CHCl_3$), only the halide ion is available as a nucleophile to attack the halonium ion. A dihalide results. But when an alkene reacts with a halogen in the presence of a nucleophilic solvent such as water, a solvent molecule is the most likely nucleophile to attack the halonium ion. When a water molecule attacks the halonium ion, the final product is a halohydrin, with a halogen on one carbon atom and a hydroxyl group on the adjacent carbon. The product may be a *chlorohydrin*, a *bromohydrin*, or an *iodohydrin*, depending on the halogen.



chlorohydrin（氯代醇） bromohydrin（溴代醇） iodohydrin（碘代醇）

Stereochemistry of Halohydrin Formation Because the mechanism involves a halonium ion, the stereochemistry of addition is anti, as in halogenation. For example, the addition of bromine water to cyclopentene gives *trans*-2-bromocyclopentanol, the product of anti addition across the double bond.



cyclopentene

trans-2-bromocyclopentanol
（反-2-溴环戊醇）
(cyclopentene bromohydrin)

Orientation of Halohydrin Formation Even though a halonium ion is involved, rather than a carbocation, the extended version of Markovnikov's rule applies to halohydrin formation. When propene reacts with chlorine water, the major product has the electrophile (the chlorine atom) bonded to the less substituted carbon of the double bond. The nucleophile (the hydroxyl group) is bonded to the more substituted carbon.

$$H_2C{=}CH{-}CH_3 + Cl_2 + H_2O \longrightarrow \underset{Cl}{H_2C}{-}\underset{OH}{CH}{-}CH_3 + HCl$$

The Markovnikov orientation observed in halohydrin formation is explained by the structure of the halonium ion intermediate. The two carbon atoms bonded to the halogen have partial positive charges, with a larger charge (and a weaker bond to the halogen) on the more substituted carbon atom (Figure 9-4). The nucleophile (water) attacks this more substituted, more electrophilic carbon atom. The result is both anti stereochemistry and Markovnikov orientation.

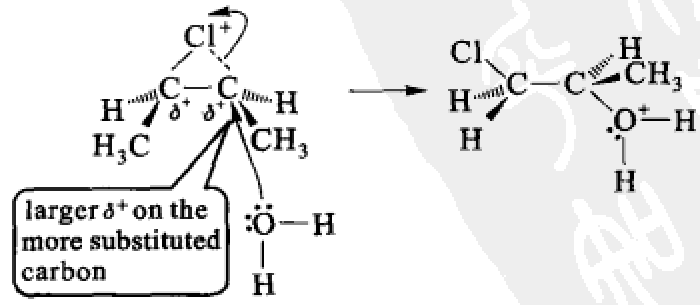


Figure 9-4 Orientation of halohydrin formation. The more substituted carbon of the chloronium ion bears more positive charge than the less substituted carbon. Attack by water occurs on the more substituted carbon to give the Markovnikov product.

This halonium ion mechanism can be used to explain and predict a wide variety of reactions in both nucleophilic and non-nucleophilic sol-

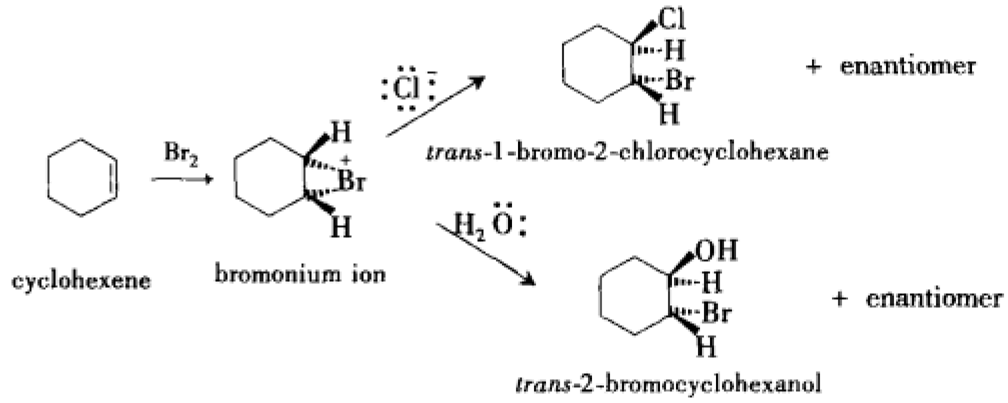
vents. The halonium ion mechanism is similar to the mercurinium ion mechanism for oxymercuration of an alkene with Markovnikov orientation.

SOLVED PROBLEM 9-2

When cyclohexene is treated with bromine in saturated aqueous sodium chloride, a mixture of *trans*-2-bromocyclohexanol and *trans*-1-bromo-2-chlorocyclohexane results. Propose a mechanism to account for these two products.

SOLUTION

Cyclohexene reacts with bromine to give a bromonium ion, which will react with any available nucleophile. The most abundant nucleophiles in saturated aqueous sodium chloride solution are water and chloride ions. Attack by water gives the bromohydrin, and attack by chloride gives the dihalide. Either of these attacks gives anti stereochemistry.



PROBLEM 9-16

Predict the major product(s) for each reaction. Include stereochemistry where appropriate.

(a) 1-methylcyclopentene + Cl_2/H_2O
(b) 2-methyl-2-butene + Br_2/H_2O
(c) *cis*-2-butene + Cl_2/H_2O
(d) *trans*-2-butene + Cl_2/H_2O
(e) 1-methylcyclopentene + Br_2 in saturated aqueous NaCl

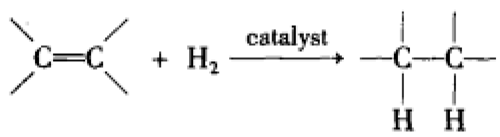
PROBLEM 9-17

Show how you would accomplish the following synthetic conversions.

(a) 3-methyl-2-pentene → 2-chloro-3-methyl-3-pentanol
(b) chlorocyclohexane → *trans*-2-chlorocyclohexanol
(c) 1-methylcyclopentanol → 2-chloro-1-methylcyclopentanol

9-10 Catalytic Hydrogenation of Alkenes

Although we have mentioned **catalytic hydrogenation** before (Sections 8-5 and 9-1), we now consider the mechanism and stereochemistry in more detail. Hydrogenation of an alkene is formally a reduction, with H_2 adding across the double bond to give an alkane. The process usually requires a catalyst containing Pt, Pd, or Ni.



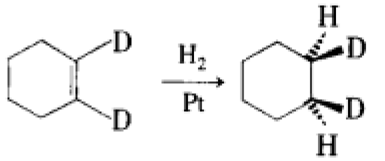
Example

$$CH_3—CH═CH—CH_3 + H_2 \xrightarrow{Pt} CH_3—CH_2—CH_2—CH_3$$

For most alkenes, hydrogenation takes place at room temperature, using hydrogen gas at atmospheric pressure. The alkene is usually dissolved in an alcohol, an alkane, or acetic acid. A small amount of platinum, palladium, or nickel catalyst is added, and the container is shaken or stirred while the reaction proceeds. Hydrogenation actually takes place at the surface of the metal, where the liquid solution of the alkene comes into contact with hydrogen and the catalyst.

Hydrogen gas is adsorbed onto the surface of these metal catalysts, and the catalyst weakens the H—H bond. In fact, if H_2 and D_2 are mixed in the presence of a platinum catalyst, the two isotopes quickly scramble to produce a random mixture of HD, H_2, and D_2. (No scrambling occurs in the absence of the catalyst.) Hydrogenation is an example of **heterogeneous catalysis**, because the (solid) catalyst is in a different phase from the reactant solution. In contrast, **homogeneous catalysis** involves reactants and catalyst in the same phase, as in the acid-catalyzed dehydration of an alcohol.

Because the two hydrogen atoms add from a solid surface, they add with **syn** stereochemistry. For example, when 1,2-dideuteriocyclohexene is treated with hydrogen gas over a catalyst, the product is the cis isomer resulting from syn addition (Figure 9−5).



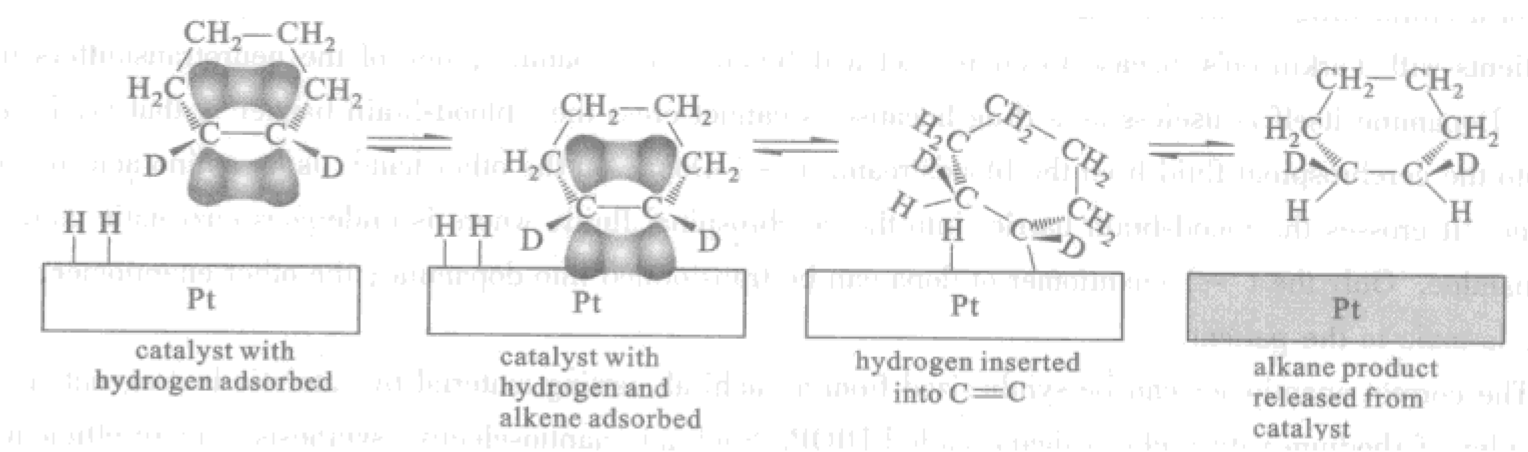
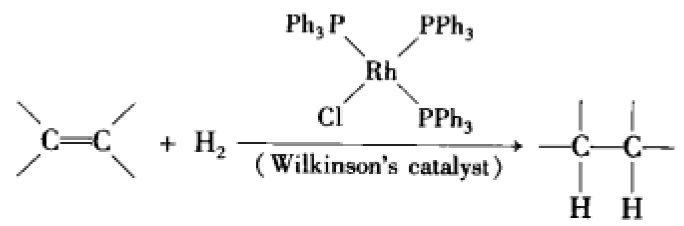


Figure 9−5 Syn stereochemistry in catalytic hydrogenation. A solid heterogeneous catalyst adds two hydrogen atoms to the same face of the pi bond (syn stereochemistry).

One face of the alkene pi bond binds to the catalyst, which has hydrogen adsorbed on its surface. Hydrogen inserts into the pi bond, and the product is freed from the catalyst. Both hydrogen atoms add to the face of the double bond that is complexed with the catalyst.

Soluble homogeneous catalysts, such as *Wilkinson's catalyst*, also catalyze the hydrogenation of carbon-carbon double bonds.



Wilkinson's catalyst is not chiral, but its triphenylphosphine (PPh_3) ligands can be replaced by chiral ligands to

give chiral catalysts that are capable of converting optically inactive starting materials to optically active products. Such a process is called **asymmetric induction** or **enantioselective synthesis**. For example, Figure 9-6 shows a chiral ruthenium complex catalyzing an enantioselective hydrogenation of a carbon-carbon double bond to give a large excess of one enantiomer. Because the catalyst is chiral, the transition states leading to the two enantiomers of product are diastereomeric. They have different energies, and the transition state leading to the (*R*) enantiomer is favored. Ryoji Noyori and William Knowles shared the 2001 Nobel Prize in chemistry for their work on chirally catalyzed hydrogenation reactions.

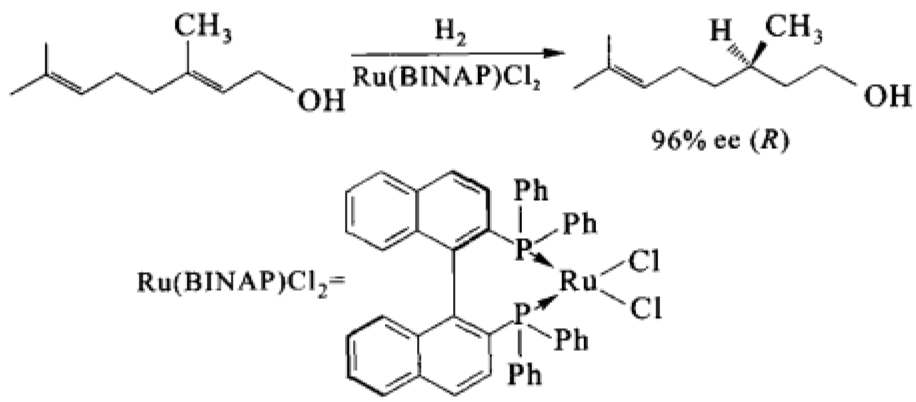
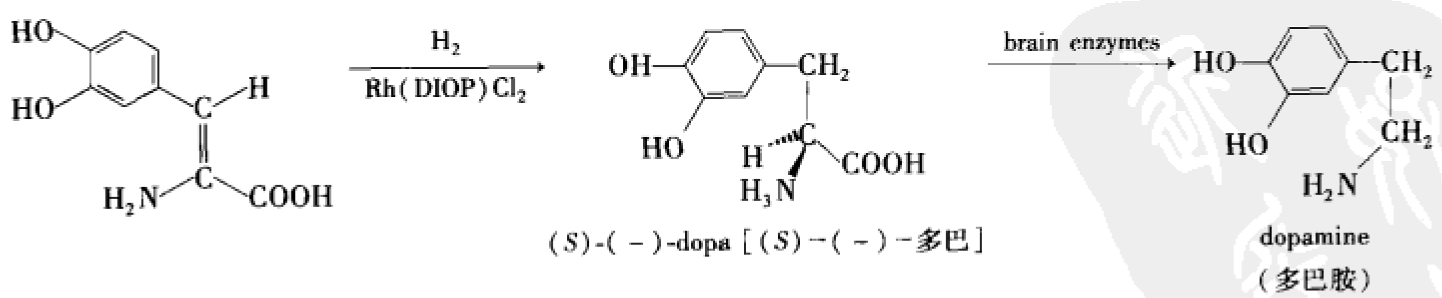
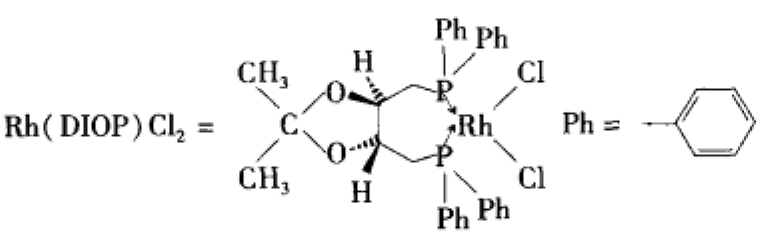


Figure 9-6 Chiral hydrogenation catalysts. Rhodium and ruthenium phosphines are effective homogeneous catalysts for hydrogenation. Chiral ligands can be attached to accomplish asymmetric induction, the creation of a new asymmetric carbon as mostly one enantiomer.

Enantioselective synthesis is particularly important in the pharmaceutical industry, because only one enantiomer of a chiral drug is likely to have the desired effect. For example, levodopa [(−)-dopa of *l*-dopa] is used in patients with Parkinson's disease to counteract a deficiency of dopamine, one of the neurotransmitters in the brain. Dopamine itself is useless as a drug because is cannot cross the "blood-brain barrier"; that is, it cannot get into the cerebrospinal fluid from the bloodstream. (−)-Dopa, on the other hand, is an amino acid related to tyrosine. It crosses the blood-brain barrier into the cerebrospinal fluid, where is undergoes enzymatic conversion to dopamine. Only the (−) enantiomer of dopa can be transformed into dopamine; the other enantiomer, (+)-dopa, is toxic to the patient.

The correct enantiomer can be synthesized from an achiral starting material by catalytic hydrogenation using a complex of rhodium with a chiral ligand called DIOP. Such an enantioselective synthesis is more efficient than making a racemic mixture, resolving it into enantiomers, and discarding the unwanted enantiomer.

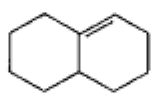
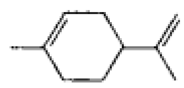




PROBLEM 9-18

Give the expected major product for each reaction, including stereochemistry where applicable.

(a) 1-butene + H_2/Pt **(b)** *cis*-2-butene + H_2/Ni

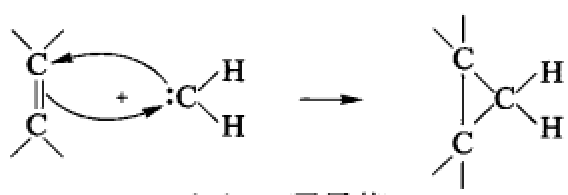
(c)  + H_2/Pt **(d)**  + excess H_2/Pt

PROBLEM 9-19

The chiral BINAP ligand shown in Figure 9-6 contains no asymmetric carbon atoms. Explain how this ligand is chiral.

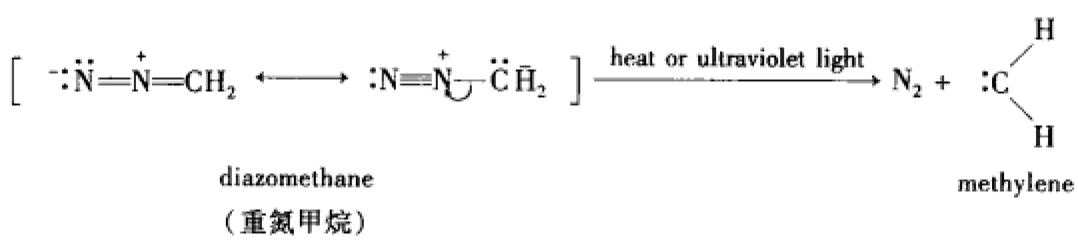
9-11 Addition of Carbenes to Alkenes

Methylene ($:CH_2$) is the simplest of the **carbenes**: uncharged, reactive intermediates that have a carbon atom with two bonds and two nonbonding electrons. Like borane (BH_3), methylene is a potent electrophile because it has an unfilled octet. It adds to the electron-rich pi bond of an alkene to form a cyclopropane.

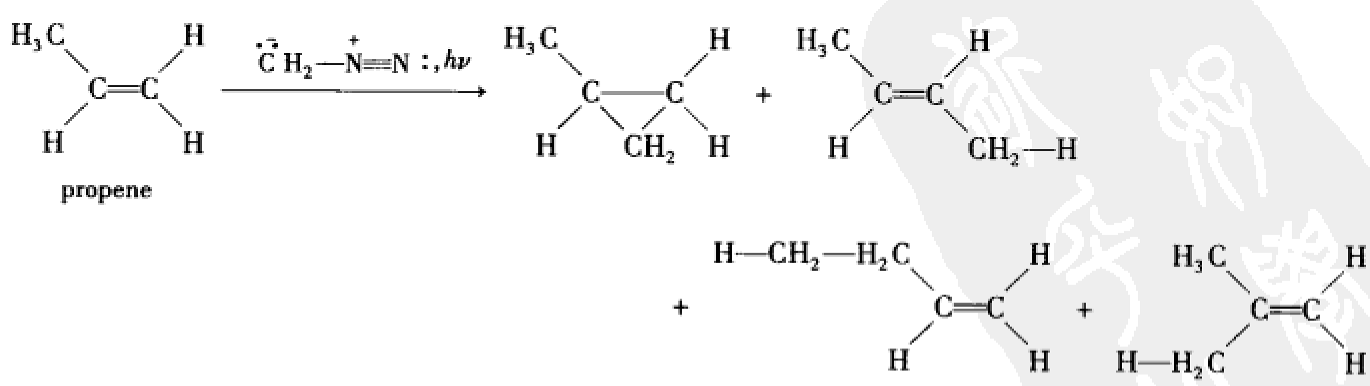


methylene (亚甲基)

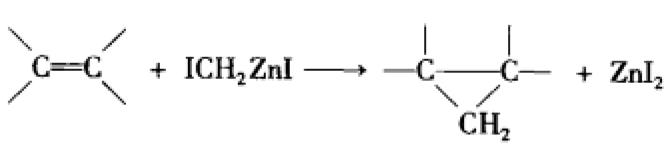
Heating or photolysis of diazomethane gives nitrogen gas and methylene:



Two difficulties arise when using diazomethane to cyclopropanate double bonds. First, it is extremely toxic and explosive. A safer reagent would be more convenient for routine use. Second, methylene generated from diazomethane is so reactive that is inserts into C—H bonds as well as C=C bonds. In the reaction of propene with diazomethane-generated methylene, for example, several side products are formed.



9-11A The Simmons-Smith Reaction



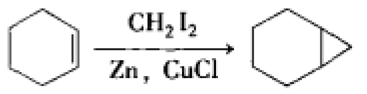
Two DuPont chemists discovered a reagent that converts alkenes to cyclopropanes in better yields than diazometh-

ane, with fewer side reactions. The **Simmons-Smith reaction**, named in their honor, is one of the best ways of making cyclopropanes.

The Simmons-Smith reagent is made by adding methylene iodide to the "zinc-copper couple," zinc dust that has been activated with an impurity of copper. The regent probably resembles iodomethyl zinc iodide, ICH_2ZnI. This kind of reagent is called a *carbenoid* because it reacts much like a carbene, but it does not actually contain a divalent carbon atom.

$$CH_2I_2 + Zn(Cu) \longrightarrow \underset{\text{Simmons-Smith reagent (a carbenoid)}}{ICH_2ZnI}$$

Simmons-Smith reagent
(a carbenoid)(类卡宾)



(59%)

9-11B Formation of Carbenes by Alpha Elimination

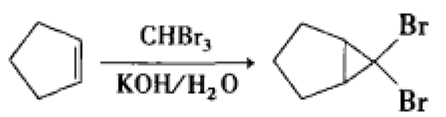
Carbenes are also formed by reactions of halogenated compounds with bases. If a carbon atom has bonds to at least one hydrogen and to enough halogen atoms to make the hydrogen slightly acidic, it may be possible to form a carbene. For example, bromoform ($CHBr_3$) reacts with a 50% aqueous solution of potassium hydroxide to form dibromocarbene.

$$\underset{\text{bromoform}}{CHBr_3} + K^+ \, ^-OH \rightleftharpoons \, ^-\!:CBr_3 \quad K^+ + H_2O$$

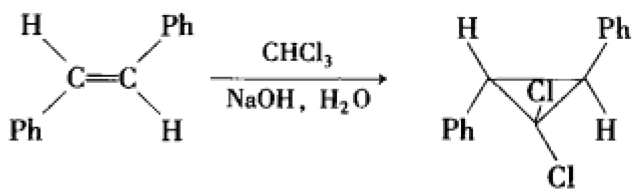
$$Br{-}\ddot{C}^-{-}Br \;(\text{with } Br \text{ below}) \rightleftharpoons \underset{\text{dibromocarbene}}{:CBr_2} + :Br^-$$

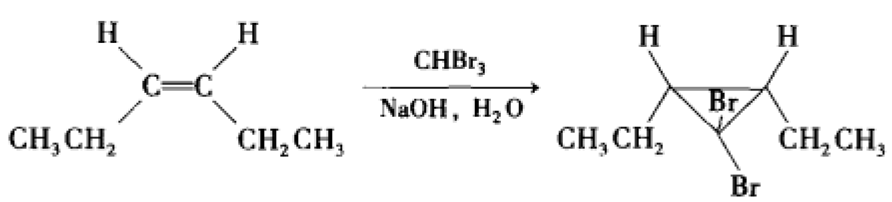
(二溴卡宾)

This dehydrohalogenation is called an **alpha elimination** (α elimination) because the hydrogen and the halogen are lost form the same carbon atom. The more common dehydrohalogenations (to form alkenes) are called **beta eliminations** because the hydrogen and the halogen are lost from adjacent carbon atoms. Dibromocarbene formed from $CHBr_3$ can add to a double bond to form a dibromocyclopropane.



The products of these cyclopropanations retain any cis or trans stereochemistry of the reactants.

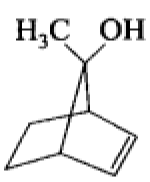
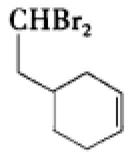




PROBLEM 9-20

Predict the major products of the following reactions.

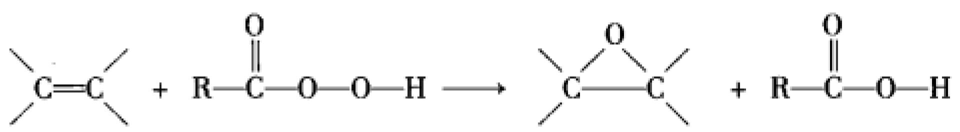
(a) cyclohexene + $CHCl_3$, 50% $NaOH/H_2O$

(b)  + CH_2I_2, Zn(Cu) (c)  + 50% $NaOH/H_2O$

9-12 Epoxidation of Alkenes

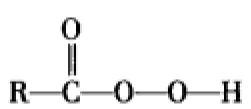
Some of the most important reactions of alkenes involve oxidation. When we speak of oxidation, we usually mean reactions that form carbon-oxygen bonds. (Halogens are oxidizing agents, and the addition of a halogen molecule across a double bond is formally an oxidation as well.) Oxidations are particularly important because many common functional groups contain oxygen, and alkene oxidations are some of the best methods for introducing oxygen into organic molecules. We will consider methods for epoxidation, hydroxylation, and oxidative cleavage of alkene double bonds.

An **epoxide** is a three-membered cyclic ether, also called an **oxirane**. Epoxides are valuable synthetic intermediates used for converting alkenes to a variety of other functional groups. An alkene is converted to an epoxide by a **peroxyacid**, a carboxylic acid that has an extra oxygen atom in a —O—O— (peroxy) linkage.

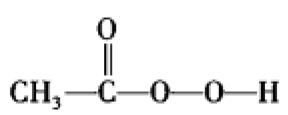


alkene peroxyacid (过氧酸) epoxide (oxirane) (环氧化物) acid

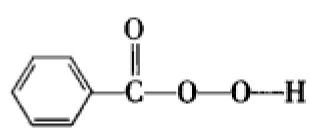
The **epoxidation** of an alkene is clearly an oxidation, since an oxygen atom is added. Peroxyacids are highly selective oxidizing agents. Some simple peroxyacids (sometimes called *peracids*) and their corresponding carboxylic acids are shown next.



a peroxyacid



peroxyacetic acid (过氧乙酸)

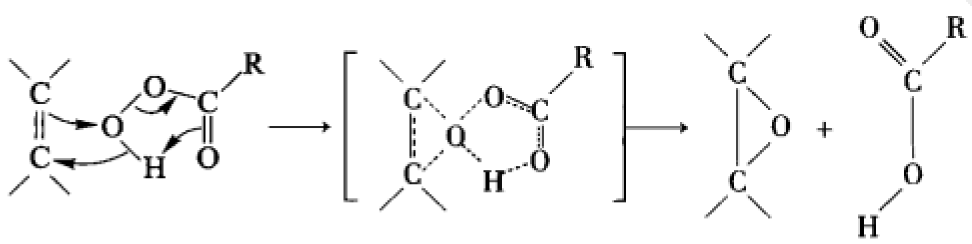


peroxybenzoic acid, $PhCO_3H$ (过氧苯甲酸)

A peroxyacid epoxidizes an alkene by a concerted electrophilic reaction where several bonds are broken and several are formed at the same time. Starting with the alkene and the peroxyacid, a one-step reaction gives the epoxide and the acid directly, without any intermediates.

MECHANISM 9-9 Epoxidation of Alkenes

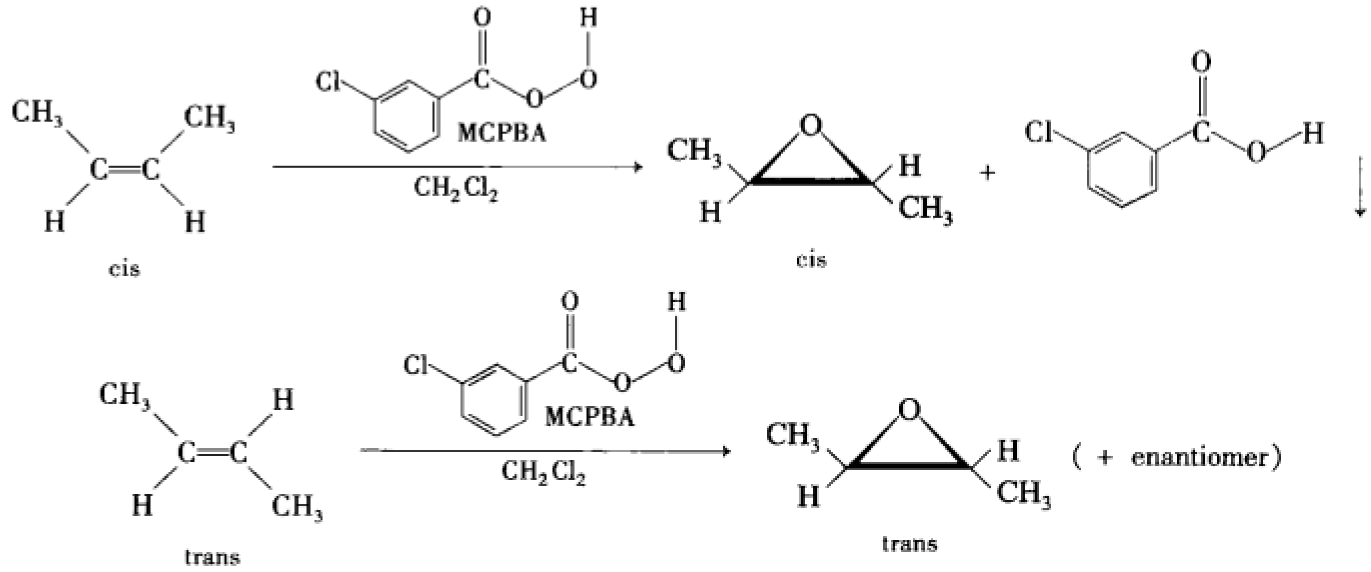
Peroxyacids epoxidize alkenes in a one-step (concerted) process.



alkene peroxyacid transition state epoxide acid

Because the epoxidation takes place in one step, there is no opportunity for the alkene molecule to rotate and change its cis or trans geometry. The epoxide retains whatever stereochemistry is present in the alkene.

The following examples use *m*-chloroperoxybenzoic acid (MCPBA), a common epoxidizing reagent, to convert alkenes to epoxides having the same cis or trans stereochemistry. MCPBA is used for its desirable solubility properties: The peroxyacid dissolves, then the spent acid precipitates out of solution.



PROBLEM 9-21

Predict the products, including stereochemistry where appropriate, for the *m*-chloroperoxybenzoic acid epoxidations of the following alkenes.

(a) *cis*-2-hexene
(b) *trans*-2-hexene
(c) *cis*-cyclodecene
(d) *trans*-cyclodecene

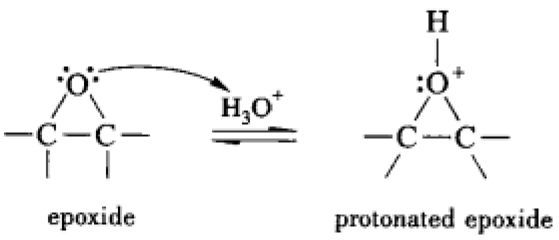
9-13 Acid-Catalyzed Opening of Epoxides

Most epoxides are easily isolated as stable products if the solution is not too acidic. Any moderately strong acid protonates the epoxide, however. Water attacks the protonated epoxide, opening the ring and forming a 1,2-diol, commonly called a **glycol.**

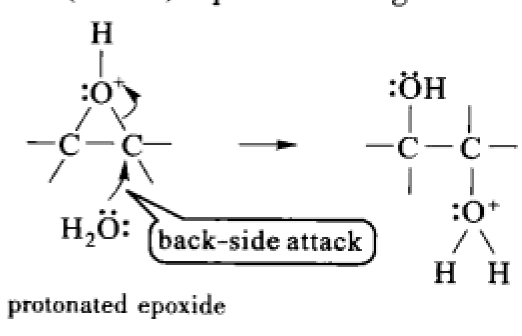
MECHANISM 9-10 Acid-Catalyzed Opening of Epoxides

The crucial step is a back-side attack by the solvent on the protonated epoxide.

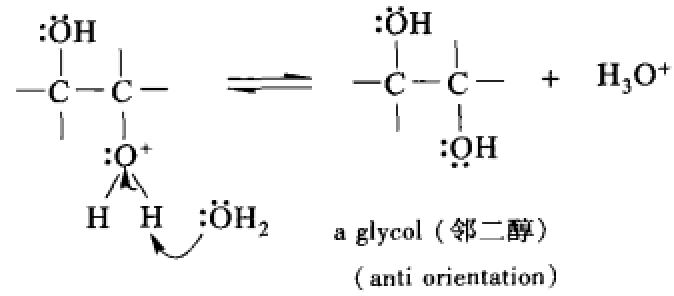
***Step 1*:** Protonation of the epoxide activates it toward nucleophilic attack.



***Step 2*:** Back-side attack by the solvent (water) opens the ring.

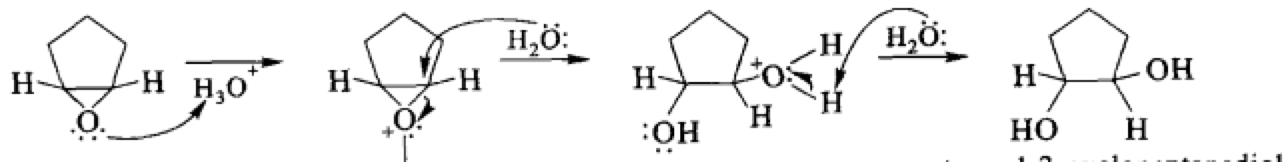


Step 3: Deprotonation gives the diol product.



a glycol (邻二醇)
(anti orientation)

Because glycol formation involves a back-side attack on a protonated epoxide, the result is anti orientation of the hydroxyl groups on the double bond. For example, when 1,2-epoxycyclopentane ("cyclopentene oxide") is treated with dilute mineral acid, the product is pure *trans*-1,2-cyclopentanediol.



cyclopentene oxide
(环氧环戊烷)

trans-1,2-cyclopentanediol
(racemic)
(反-1,2-环戊二醇)

PROBLEM 9-22

(a) Propose a detailed mechanism for the conversion of *cis*-3-hexene to the epoxide (3,4-epoxyhexane) and the ringopening reaction to give the glycol, 3,4-hexanediol. In your mechanism, pay particular attention to the stereochemistry of the intermediates and products.

(b) Repeat part (a) for *trans*-3-hexene. Compare the products obtained from *cis*-and *trans*-3-hexene. Is this reaction sequence stereospecific?

Epoxidation regents can be chosen to favor either the epoxide or the glycol. Peroxyacetic acid is used in strongly acidic water solutions. The acidic solution protonates the epoxide and converts it to the glycol. Peroxybenzoic acids are weak acids that can be used in nonnucleophilic solvents such as carbon tetrachloride. *m*-Chloroperoxybenzoic acid in CCl_4 generally gives good yields of epoxides. Figure 9-7 compares the uses of these reagents.

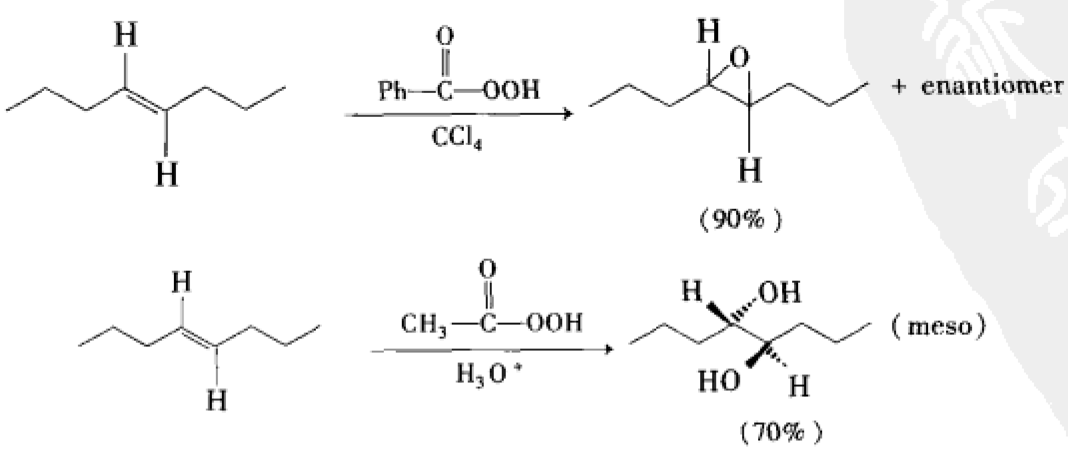


Figure 9-7 Reagents for epoxidation. Peroxyacetic acid is used in strongly acidic aqueous solutions. Alkenes are epoxidized, then opened to glycols in one step. Weakly acidic peroxyacids, such as peroxybenzoic acid, can be used in nonaqueous solutions to give good yields of epoxides.

PROBLEM 9-23

Predict the major products of the following reactions.

(a) *cis*-2-hexene + MCPBA in chloroform

(b) *trans*-3-hexene + peroxyacetic acid (CH_3CO_3H) in water

(c) *trans*-cyclodecene + peroxyacetic acid in water

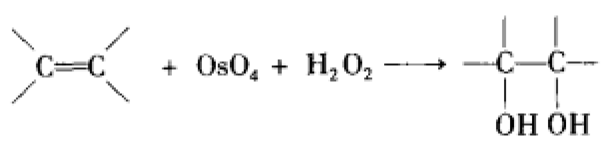
(d) *cis*-cyclodecene + MCPBA in CH_2Cl_2, then dilute aqueous acid

PROBLEM 9-24

When 1,2-epoxycyclohexane (cyclohexene oxide) is treated with anhydrous HCl in methanol, the principal product is *trans*-2-methoxycyclohexanol. Propose a mechanism to account for the formation of this product.

9-14 Syn Hydroxylation of Alkenes

Converting an alkene to a glycol requires adding a hydroxyl group to each end of the double bond. This addition is called **hydroxylation** of the double bond. We have seen that epoxidation of an alkene, followed by acidic hydrolysis, gives *anti* hydroxylation of the double bond. Reagents are also available for the hydroxylation of alkenes with *syn* stereochemistry. The two most common reagents for this purpose are osmium tetroxide and potassium permanganate.

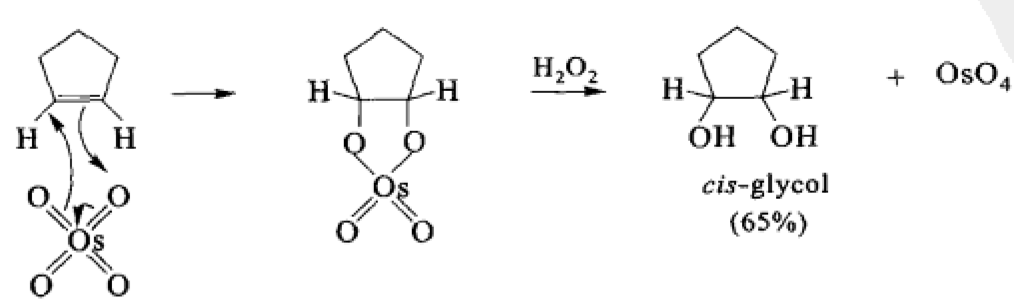


(*or* $KMnO_4$, ^-OH) syn addition

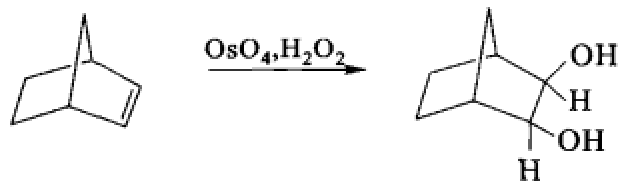
9-14A Osmium Tetroxide Hydroxylation

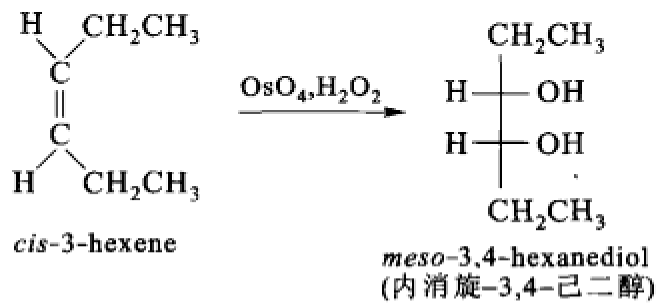
Osmium tetroxide (OsO_4, sometimes called *osmic acid*) reacts with alkenes in a concerted step to form a cyclic osmate ester. Hydrogen peroxide hydrolyzes the osmateester and reoxidizes osmium to osmium tetroxide. The regenerated osmium tetroxide catalyst continues to hydroxylate more molecules of the alkene.

Because the two carbon-oxygen bonds are formed simultaneously with the cyclicosmate ester, the oxygen atoms add to the same face of the double bond; that is, they add with syn stereochemistry. The following reactions show the use of OsO_4 and H_2O_2 for the syn hydroxylation of alkenes.



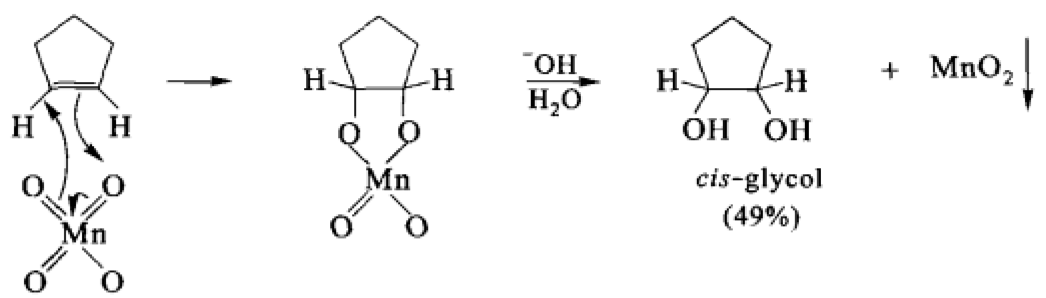
concerted formation of osmate ester





9-14B Permanganate Hydroxylation

Osmium tetroxide is expensive, highly toxic, and volatile. A cold, dilute solution of potassium permanganate ($KMnO_4$) also hydroxylates alkenes with syn stereochemistry, with slightly reduced yields in most cases. Like osmium tetroxide, permanganate adds to the alkene double bond to form a cyclic ester: a manganate ester in this case. The basic solution hydrolyzes the manganate ester, liberating the glycol and producing a brown precipitate of manganese dioxide, MnO_2.



concerted formation of manganate ester (协同作用形成锰酸酯)

In addition to its synthetic value, the permanganate oxidation of alkenes provides a simple chemical test for the presence of an alkene. When an alkene is added to a clear, deep purple aqueous solution of potassium permanganate, the solution loses its purple color and becomes the murky, opaque brown color of MnO_2. (Although there are other functional groups that decolorize permanganate, few do it as quickly as alkenes.)

9-14C Choosing a Reagent

To hydroxylate an alkene with syn stereochemistry, which is the better reagent: osmium teroxide or potassium permanganate? Osmium tetroxide gives better yields, but permanganate is cheaper and safer to use. The answer depends on the circumstances.

If the starting material is only 2 mg of a compound 15 steps along in a difficult synthesis, we use osmium tetroxide. The better yield is crucial because the starting material is precious and expensive, and little osmic acid is needed. If the hydroxylation is the first step in a synthesis and involves 5 kg of the starting material, we use potassium permanganate. The cost of buying enough osmium tetroxide would be prohibitive, and dealing with such a large amount of a volatile, toxic reagent would be inconvenient. On such a large scale, we can accept the lower yield of the permanganate oxidation.

PROBLEM 9-25

Predict the major products of the following reactions, including stereochemistry.

(**a**) cyclohexene + $KMnO_4/H_2O$

(**b**) cyclohexene + peroxyacetic acid in water

(**c**) *cis*-2-pentene + OsO_4/H_2O_2

(**d**) *cis*-2-pentene + peroxyacetic acid in water

(e) *trans*-2-pentene + OsO_4/H_2O_2

(f) *trans*-2-pentene + peroxyacetic acid in water

PROBLEM 9-26

Show how you would accomplish the following conversions.

(a) *cis*-3-hexene to *meso*-3,4-hexanediol

(b) *cis*-3-hexene to (d,l)-3,4-hexanediol

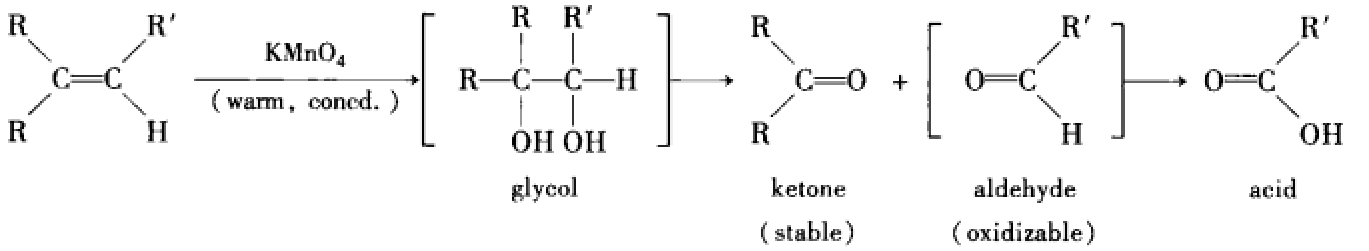
(c) *trans*-3-hexene to *meso*-3,4-hexanediol

(d) *trans*-3-hexene to (d,l)-3,4-hexanediol

9-15 Oxidative Cleavage of Alkenes

9-15A Cleavage by Permanganate

In a potassium permanganate hydroxylation, if the solution is warm or acidic or too concentrated, **oxidative cleavage** of the glycol may occur. Mixtures of ketones and carboxylic acids are formed, depending on whether there are any oxidizable aldehydes in the initial fragments. A terminal $=CH_2$ group is oxidized to CO_2 and water. Figure 9-8 shows the oxidative cleavage of a double bond by warm or concentrated permanganate.



Examples

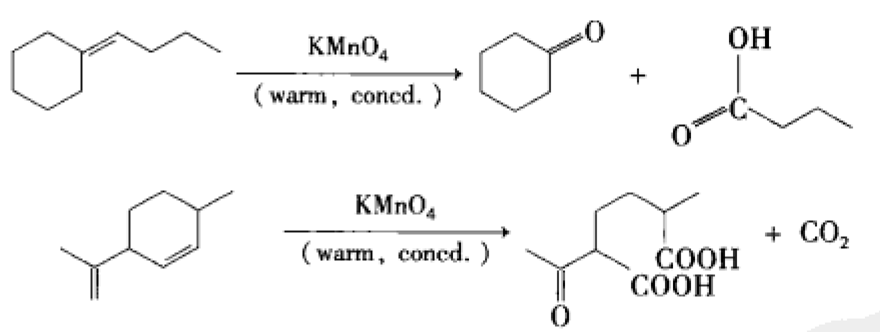
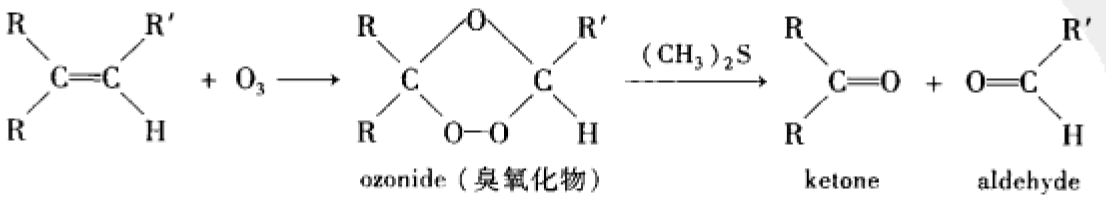


Figure 9-8 Permanganate cleavage of alkenes. Warm, concentrated $KMnO_4$ oxidizes alkenes to glycols, then cleaves the glycols. The products are initially ketones and aldehydes, but aldehydes are oxidized to carboxylic acids under these conditions.

9-15B Ozonolysis

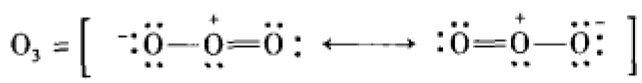
Like permanganate, ozone cleaves double bonds to give ketones and aldehydes. However, ozonolysis is milder, and both ketones and aldehydes can be recovered without further oxidation.



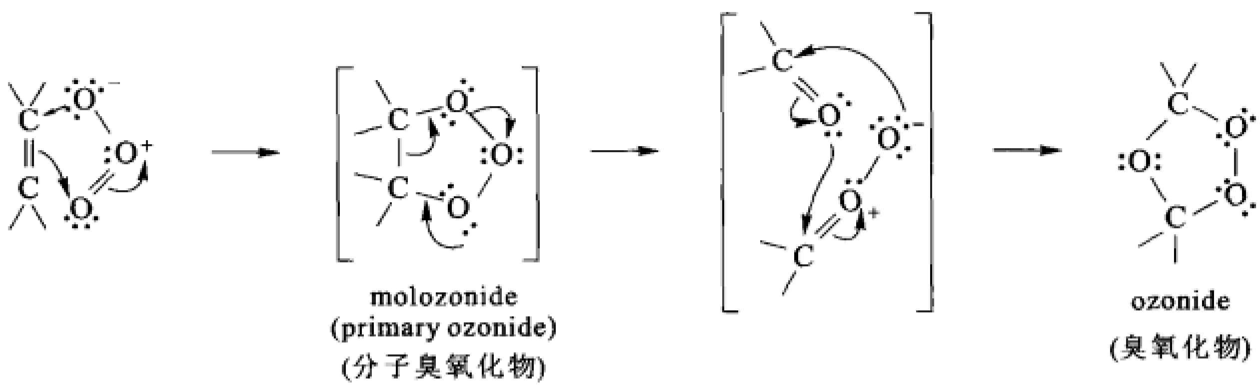
Ozone (O_3) is a high-energy form of oxygen produced when ultraviolet light or an electrical discharge passes through oxygen gas. Ultraviolet light from the sun converts oxygen to ozone in the upper atmosphere. This "ozone layer" shields the earth from some of the high-energy ultraviolet radiation it would otherwise receive.

$$\frac{3}{2}O_2 + 142\ \text{kJ} \longrightarrow O_3$$

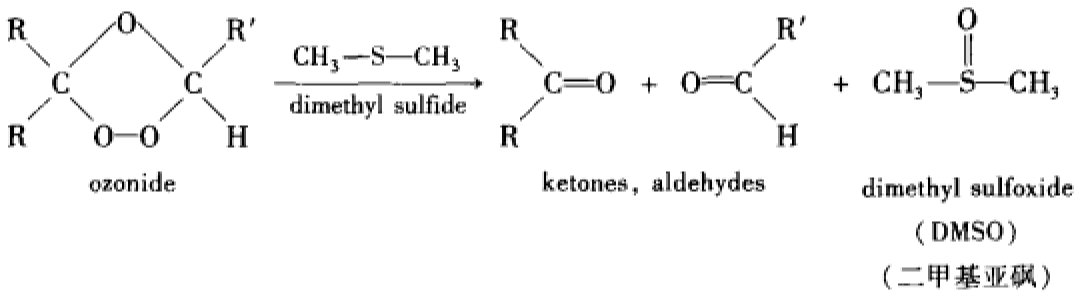
Ozone has 142 kJ/mol of excess energy over oxygen, and it is much more reactive. A Lewis structure of ozone shows that the central oxygen atom bears a positive charge, and each of the outer oxygen atoms bears half a negative charge.

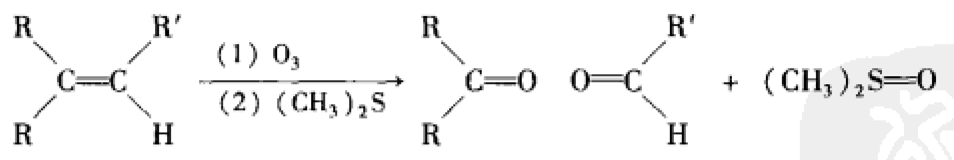


Ozone reacts with an alkene to form a cyclic compound called a *primary ozonide* or *molozonide* (because 1 mol of ozone has been added). The molozonide has two peroxy (—O—O—) linkages, so it is quite unstable. It rearranges rapidly, even at low temperatures, to form an ozonide.

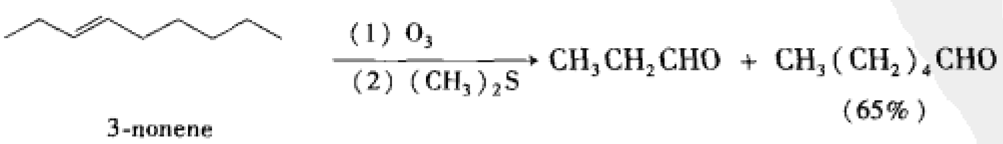


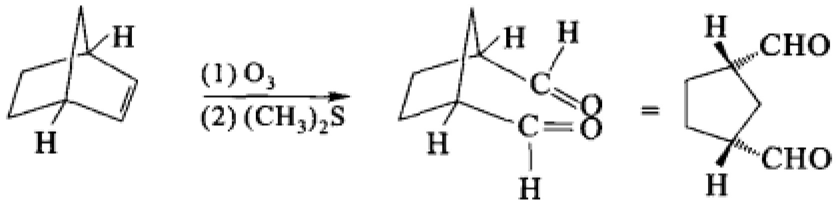
Ozonides are not very stable, and they are rarely isolated. In most cases, they are immediately reduced by a mild reducing agent such as zinc or (more recently) dimethyl sulfide. The products of this reduction are ketones and aldehydes.

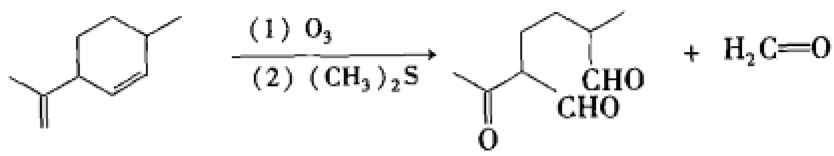




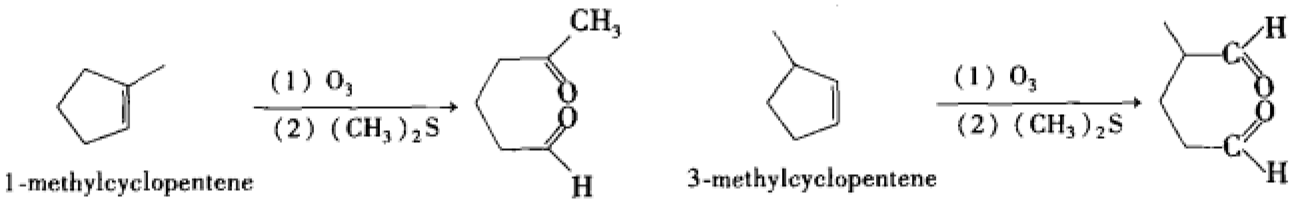
The following reactions show the products obtained from ozonolysis of some representative alkenes. Note how (1) and (2) are used with a single reaction arrow to denote the steps in a two-step sequence.







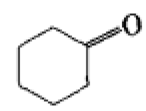
One of the most common uses of ozonolysis has been for determining the positions of double bonds in alkenes. For example, if we were uncertain of the position of the methyl group in a methylcyclopentene, the products of ozonolysis-reduction would confirm the structure of the original alkene.



PROBLEM 9-27

Give structures of the alkenes that would give the following products upon ozonolysis-reduction.

(a) $CH_3-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH_2-CH_3$

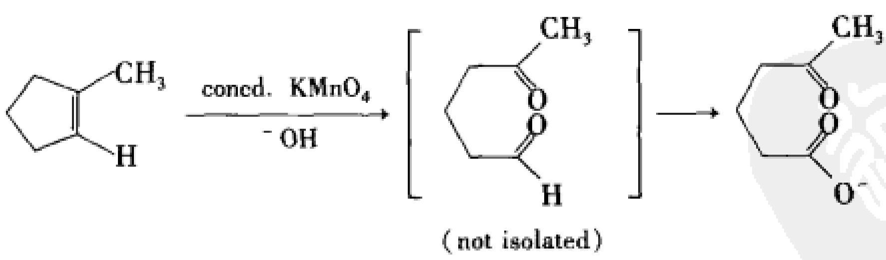
(b)  and $CH_3-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-H$

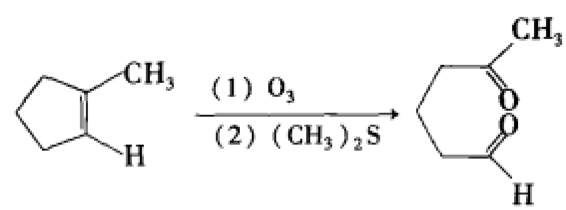
cyclohexanone

(c) $CH_3-CH_2-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-CH_2-CH_3$ and $CH_3-CH_2-\overset{O}{\overset{\|}{C}}-H$

9-15C Comparison of Permanganate Cleavage and Ozonolysis

Both permanganate and ozonolysis break the carbon-carbon double bond and replace it with carbonyl ($C{=}O$) groups. In the permanganate cleavage, any aldehyde products are further oxidized to carboxylic acids. In the ozonolysis-reduction procedure, the aldehyde products are generated in the dimethyl sulfide reduction step (and not in the presence of ozone), and they are not oxidized.



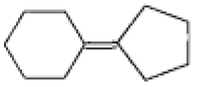


PROBLEM 9-28

Predict the major products of the following reactions.

(a) (E)-3-methyl-3-octene + ozone, then $(CH_3)_2S$

(b) (Z)-3-methyl-3-octene + warm, concentrated $KMnO_4$

(c)  + O_3, then $(CH_3)_2S$

(d) 1-ethylcycloheptene + ozone, then $(CH_3)_2S$

(e) 1-ethylcycloheptene + warm, concentrated $KMnO_4$

(f) 1-ethylcycloheptene + cold, dilute $KMnO_4$

9-16 Polymerization of Alkenes

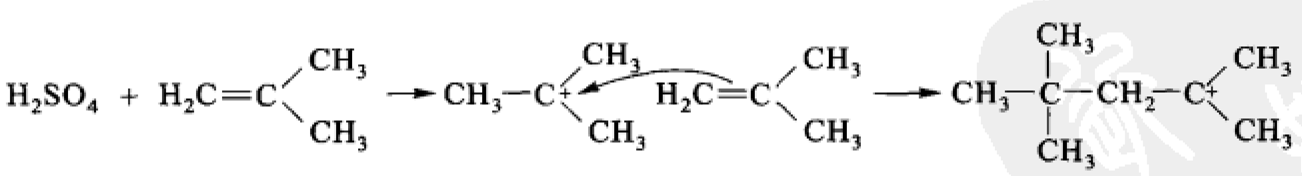
A **polymer** is a large molecule composed of many smaller repeating units (the **monomers**) bonded together. Alkenes serve as monomers for some of the most common polymers, such as polyethylene, polypropylene, polystyrene, poly(vinylchloride), and many others. Alkenes generally undergo **addition polymerization**, the rapid addition of one molecule at a time to a growing polymer chain. There is generally a reactive intermediate (cation, anion, or radical) at the growing end of the chain; for that reason, addition polymers are also called **chain-growth polymers**.

Many alkenes undergo addition polymerization under the right conditions. The chain-growth mechanism involves addition of the reactive end of the growing chain across the double bond of the alkene monomer. Depending on the structure of the monomer, the reactive intermediates may be carbocations, free radicals, or carbanions.

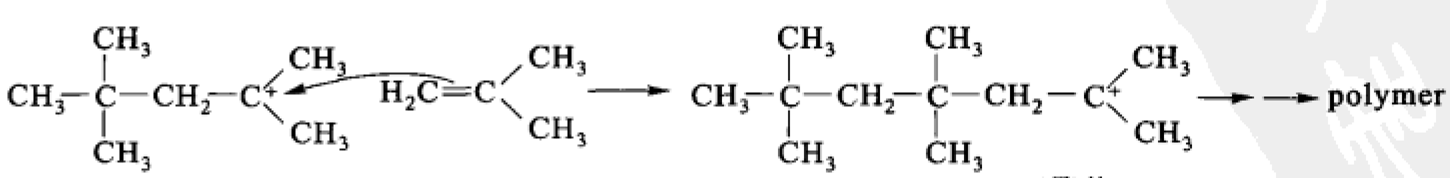
9-16A Cationic Polymerization

Alkenes that easily form carbocations are good candidates for **cationic polymerization**, which is just another example of electrophilic addition to an alkene. Consider what happens when pure isobutylene is treated with a trace of concentrated sulfuric acid. Protonation of the alkene forms a carbocation. If a large concentration of isobutylene is available, another molecule of the alkene may act as the nucleophile and attack the carbocation to form the *dimer* (two monomers joined together) and give another carbocation. If the conditions are right, the growing cationic end of the chain will keep adding across more molecules of the monomer. The polymer of isobutylene is *polyisobutylene*, one of the constituents of *butyl rubber* used in inner tubes and other synthetic rubber products.

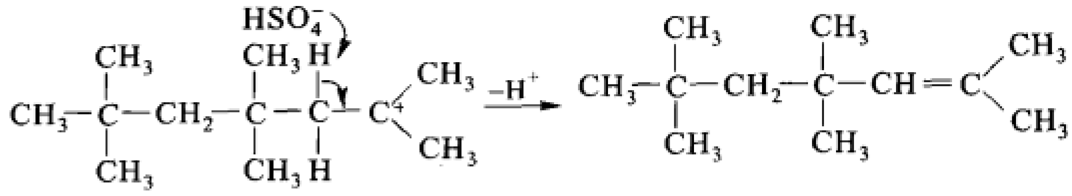
Protonation *Attack by the second molecule of isobutylene*



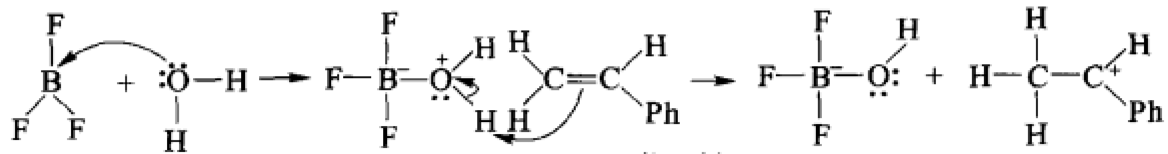
Attack by a third molecule to give a trimer



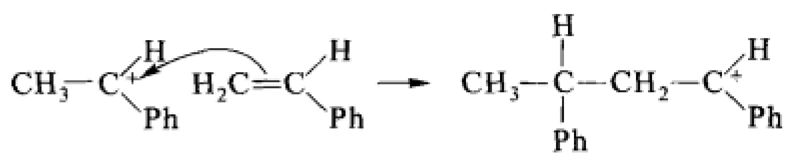
Loss of a proton is the most common side reaction that terminates chain growth:



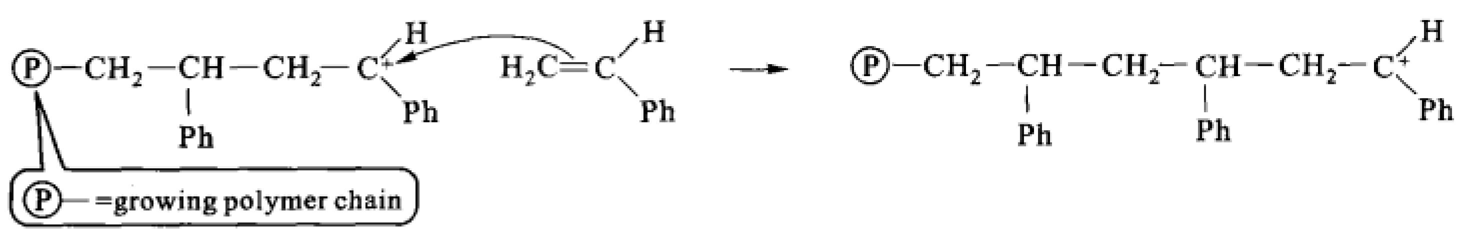
Boron trifluoride (BF_3) is an excellent catalyst for cationic polymerization because it leaves no good nucleophile that might attack a carbocation intermediate and end the polymerization. Boron trifluoride is electron-deficient and a strong Lewis acid. It usually contains a trace of water that acts as a co-catalyst by adding to BF_3 and then protonating the monomer. Protonation occurs at the less substituted end of an alkene double bond to give the more stable carbocation. Each additional monomer molecule adds with the same orientation, always giving the more stable carbocation. The following reaction shows the polymerization of styrene (vinylbenzene) using BF_3 as the catalyst.



First chain-lengthening step

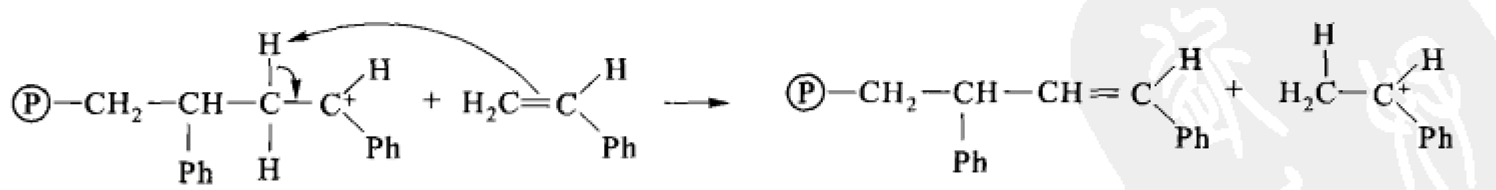


After many steps the polymerization continues



The most likely ending of this BF_3-catalyzed polymerization is the loss of a proton from the carbocation at the end of the chain. This side reaction terminates one chain, but it also protonates another molecule of styrene, initiating a new chain.

Termination of a polymer chain



The product of this polymerization is polystyrene: a clear, brittle plastic that is often used for inexpensive lenses, transparent containers, and styrofoam insulation. Polystyrene is also the major component of the resin beads that are used to make synthetic proteins.

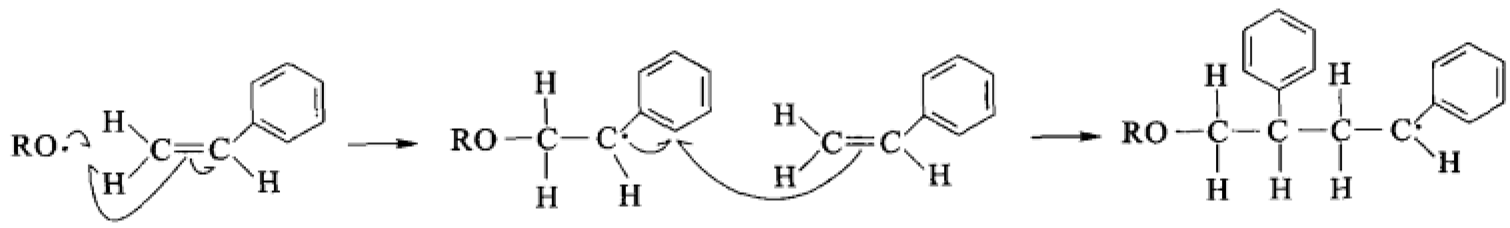
9−16B Free-Radical Polymerization

Many alkenes undergo **free-radical polymerization** when they are heated with radical initiators. For example,

styrene polymerizes to polystyrene when it is heated to 100 ℃ with a peroxide initiator. A radical adds to styrene to give a resonancestabilized radical, which then attacks another molecule of styrene to give an elongated radical.

Initiation step $\text{ROOR} \xrightarrow{\text{heat}} 2\text{RO}\cdot$

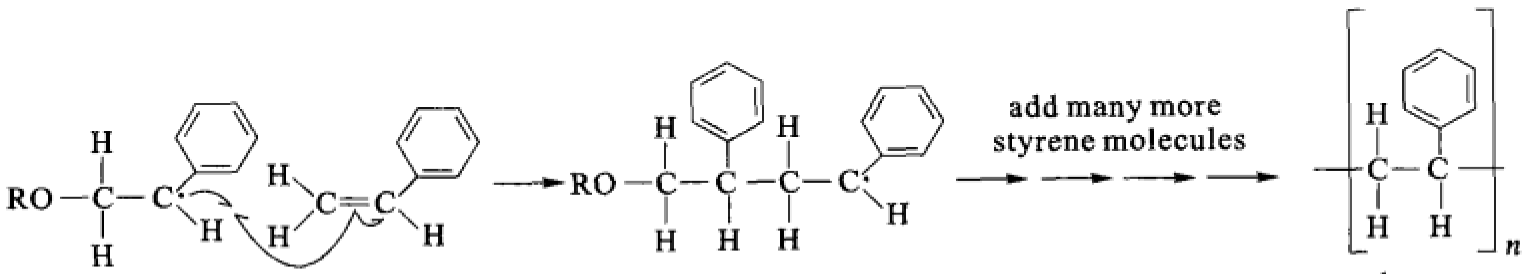
Propagation step



styrene stabilized radical styrene growing chain

Each propagation step adds another molecule of styrene to the radical end of the growing chain. This addition always takes place with the orientation that gives another resonance-stabilized benzylic (next to a benzene ring) radical.

Propagation step



growing chain styrene elongated chain polystyrene n=about 100 to 10 000

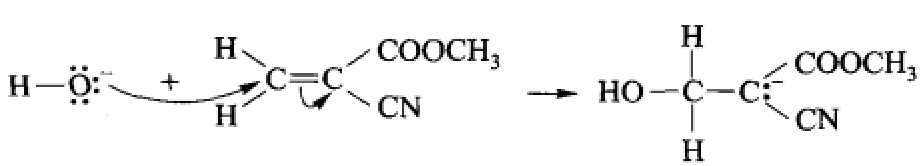
Chain growth may continue with addition of several hundred or several thousand styrene units. Eventually, the chain reaction stops, either by the coupling of two chains or by reaction with an impurity (such as oxygen) or simply by running out of monomer.

Ethylene is also polymerized by free-radical chain-growth polymerization. With ethylene, the free-radical intermediates are less stable, so stronger reaction conditions are required. Ethylene is commonly polymerized by free-radical initiators at pressures around $3\,000 \times 10^5$ Pa and temperatures of about 200 ℃. The product, called *low-density polyethylene*, is the material commonly used in polyethylene bags.

9-16C Anionic Polymerization

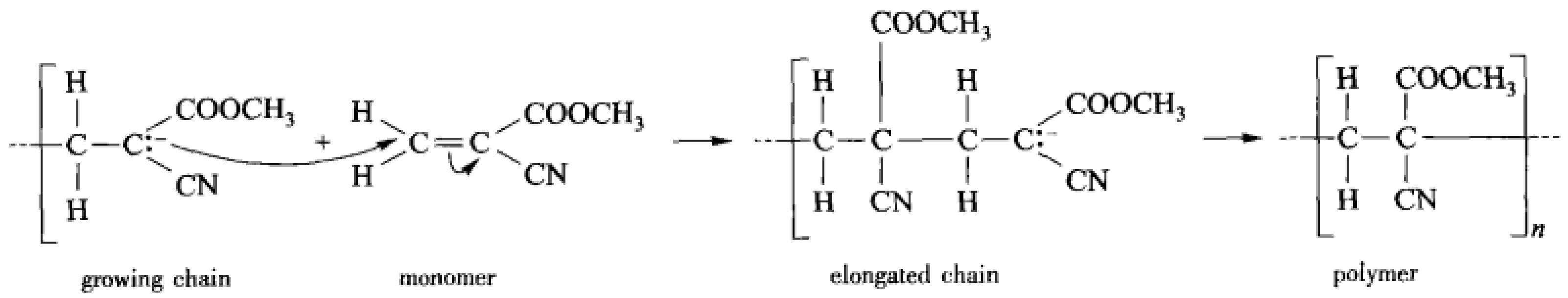
Like cationic polymerization, **anionic polymerization** depends on the presence of a stabilizing group. To stabilize anions, the double bond should have a strong electron-withdrawing group such as a carbonyl group, a cyano group, or a nitro group. Methyl α-cyanoacrylate contains two powerful electron-withdrawing groups, and it undergoes nucleophilic additions very easily. If this liquid monomer is spread in a thin film between two surfaces, traces of basic impurities (metal oxides, etc.) can catalyze its rapid polymerization. The solidified polymer joins the two surfaces. The chemists who first made this monomer noticed how easily it polymerizes and realized that it could serve as a fast-setting glue. Methyl α-cyanoacrylate is sold commercially as Super Glue.

Initiation step



trace of base Super Glue highly stabilized anion

Chain lengthening step

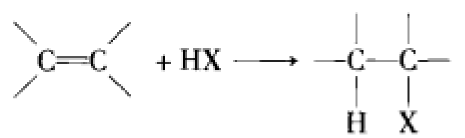


Summary in Chinese

本 章 概 要

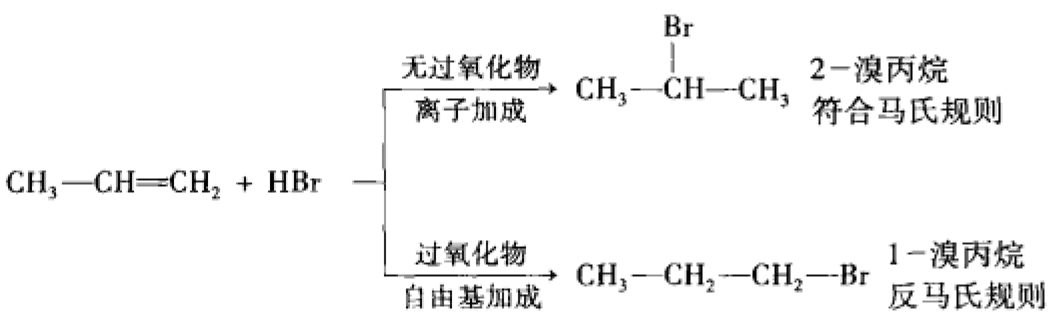
一、烯烃亲电加成反应(electrophilic additions to alkenes)

1. 加卤化氢反应(addition of hydrogen halides, Section 9-3):



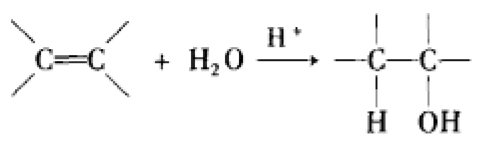
(HX = HCl, HBr, HI)

☆ 反应经过碳正离子机理,可能发生重排,无立体选择性,在不对称烯烃与卤化氢的加成反应中,酸的质子(H^+)加到含氢较多的双键碳原子上,而卤素离子加到含氢较少的双键碳原子上,符合马氏规则(Markovnikov's rule)。比较丙烯与溴化氢的离子加成和自由基加成反应:



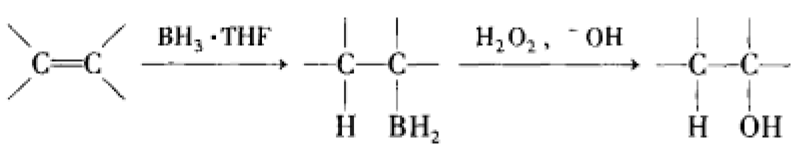
在过氧化物存在下,烯烃的溴化氢加成反应经过碳自由基机理,不对称烯烃加溴化氢得到反马氏产物。只有溴化氢有过氧化物效应,氯化氢、碘化氢无过氧化物效应。马氏规则的本质是在烯烃的亲电加成或自由基加成反应中,亲电试剂或自由基总是以能够生成最稳定的中间体(碳正离子或碳自由基)的方式加到双键碳上。

2. 酸催化加水反应(acid-catalyzed hydration, Section 9-4):



☆ 反应经过碳正离子机理,符合马氏规则,可能发生重排,无立体选择性。

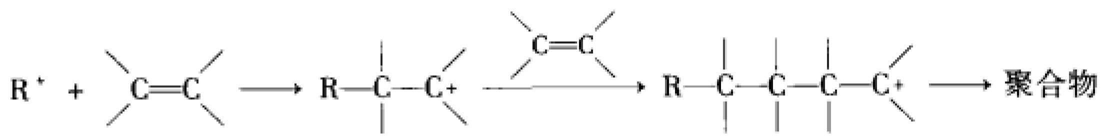
3. 硼氢化-氧化反应(hydroboration-oxidation, Section 9-7):



☆ 反应经过四元环过渡态,协同机理,得到顺式加成、反马氏规则的产物。利用此反应可从端烯烃出

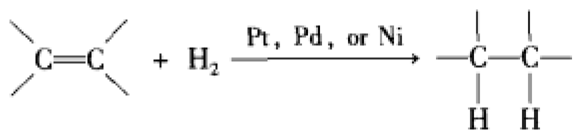
发高选择性地合成伯醇。

4. 阳离子型聚合反应(cationic polymerization, Section 9-16)



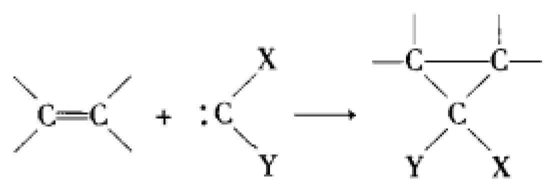
☆ 质子酸、Lewis 酸 BF_3 均可作为阳离子型聚合反应催化剂。在少量碱或过氧化物存在下亦可发生阴离子型或自由基型聚合反应。

二、烯烃还原-催化加氢反应(reduction of alkenes: catalytic hydrogenation, Section 9-10)



☆ Pt、Pd、Ni 作为催化剂,烯烃顺式加氢反应是石油工业中的重要反应。在反应体系中加入手性配体时,Ru 可催化烯烃不对称加氢反应,此类反应在药物合成中有重要的应用。

三、烯烃与卡宾加成反应:环丙烷化反应(addition of carbenes to alkenes: cyclopropanation, Section 9-11)

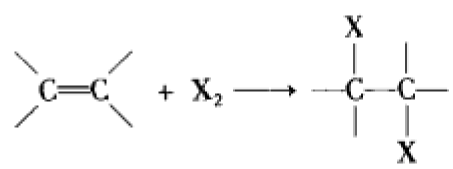


(X, Y = H, Cl, Br, I, COOEt)

☆ 试剂 N_2CH_2/加热或光照、$CHBr_3/OH^-$、$CHCl_3/OH^-$、CH_2I_2/(Zn, CuCl) (Simmons-Smith reaction, Section 9-11)均可生成卡宾,原位与烯烃双键发生加成反应,得到环丙烷衍生物。

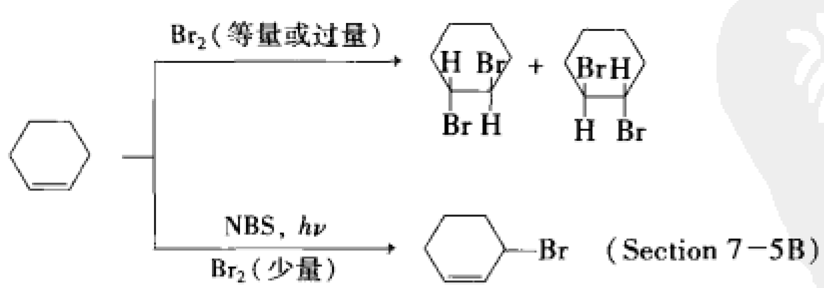
四、烯烃氧化加成(oxidation additions to alkenes)

1. 加卤素反应(addition of halogens, Section 9-8):

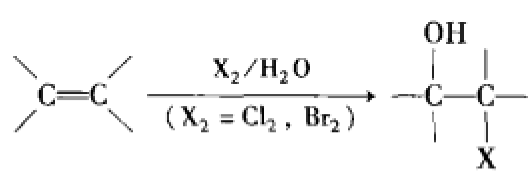


($X_2 = Cl_2, Br_2$)

☆ 反应一般经过三元环卤素鎓离子中间体,卤素反式加成,生成邻二卤代烷烃。比较溴与环己烯在不同条件下的反应:



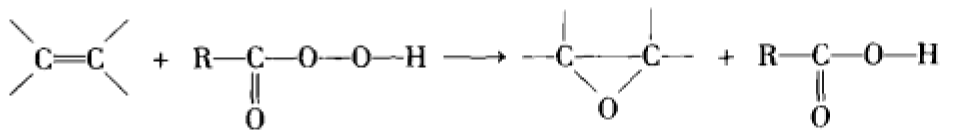
2. 加次卤酸反应:生成卤代醇(halohydrin formation, Section 9-9):



☆ 反应一般经过三元环卤素鎓离子中间体,卤素原子和羟基反式加到双键碳原子上。反应物为不对

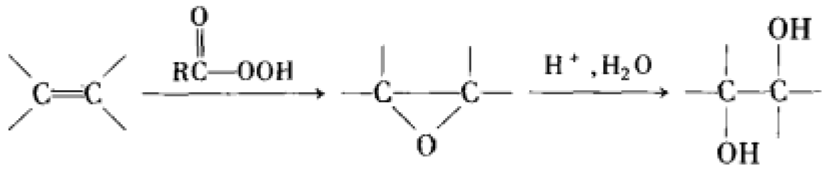
称烯烃时,卤素原子加到含氢较多的双键碳原子上,羟基加到含氢较少的双键碳原子上。

3. 环氧化反应(epoxidation,Section 9-12):

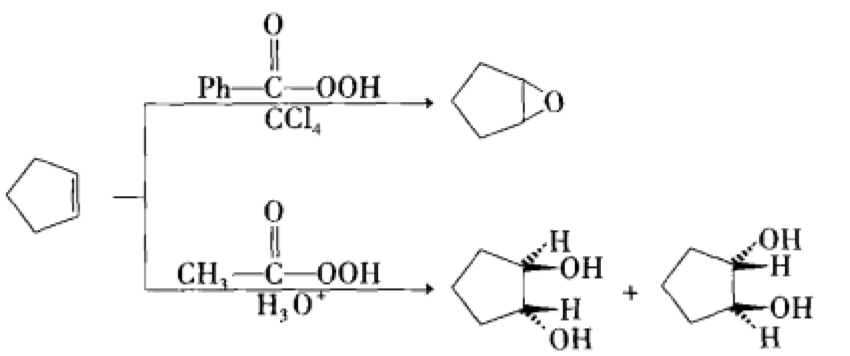


☆ 在过氧酸存在下,烯烃易发生氧化加成反应,可用于合成环氧化物。

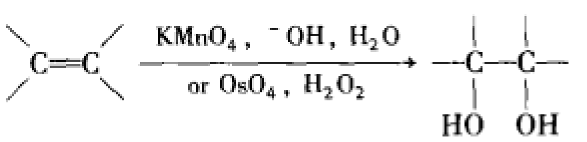
4. 反式二羟基化反应(anti hydroxylation,Section 9-13):



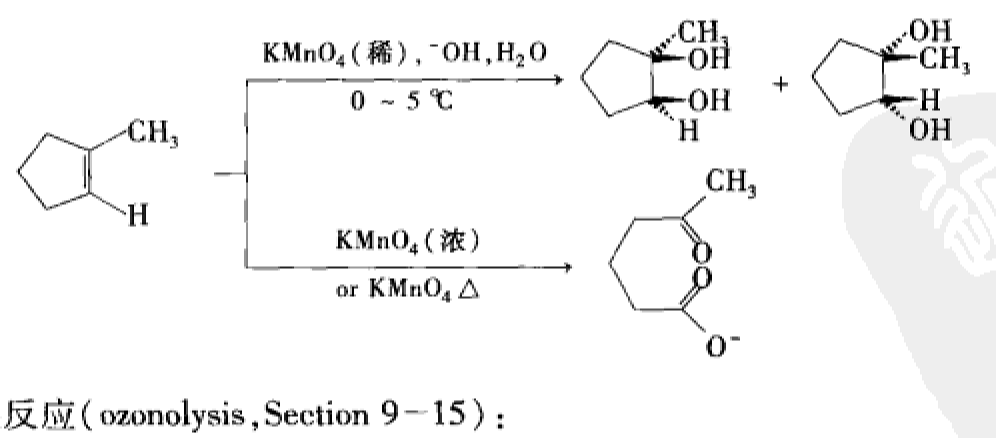
☆ 酸催化环氧化物水解开环反应,或在酸性水溶液中过氧酸与烯烃反应直接合成邻二醇衍生物,两个羟基反式加成到双键碳原子上。比较环戊烯与过氧酸在不同条件下的反应:



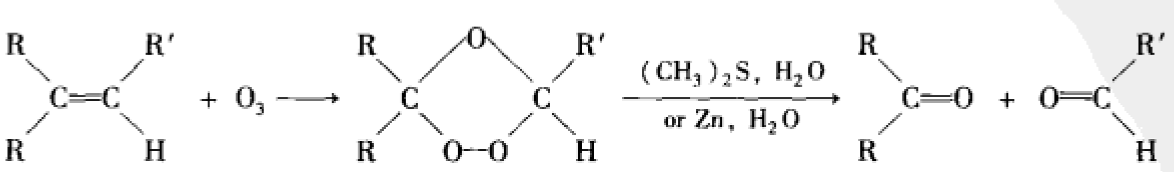
5. 顺式二羟基化反应(syn hydroxylation,Section 9-14):



☆ 反应经过五元环锰酸酯或五元环锇酸酯中间体,两个羟基顺式加成到双键碳原子上。在较低温度下,$KMnO_4$ 的碱性稀溶液氧化烯烃生成邻二醇,而 $KMnO_4$ 的浓溶液在酸性介质中或较高温度下氧化烯烃时,双键彻底断裂,得到相应的酮和/或羧酸。端烯烃的亚甲基氧化生成二氧化碳。比较1-甲基环戊烯与 $KMnO_4$ 在不同条件下的反应:



6. 臭氧氧化断裂反应(ozonolysis,Section 9-15):



☆ 臭氧氧化烯烃第一步生成五元环臭氧化物,第二步水解反应加入硫醚或锌粉,将第一步反应中生成的过氧化氢还原成水,防止醛继续氧化。此反应可用于推断烯烃的双键位置。

Essential Problem-Solving Skills in Chapter 9

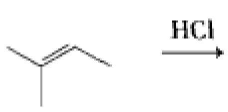
1. Predict the products of additions, oxidations, reductions, and cleavages of alkenes, including
   (a) orientation of reaction (regiochemistry),
   (b) stereochemistry.
2. Propose logical mechanisms to explain the observed products of alkene reactions, including regiochemistry and stereochemistry.
3. Use retrosynthetic analysis to solve multistep synthesis problems with alkenes as reagents, intermediates, or products.
4. When more than one method is usable for a chemical transformation, choose the better method and explain its advantages.
5. Use clues provided by products of reactions such as ozonolysis to determine the structure of an unknown alkene.

Study Problems

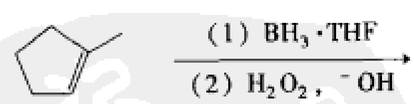
9-29 Define each term, and give an example.

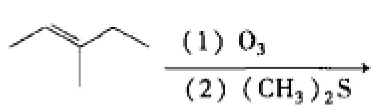
(a) dimerization(二聚)
(b) polymerization(聚合)
(c) electrophilic addition(亲电加成)
(d) stereospecific addition(立体专一性加成)
(e) syn addition(顺式加成)
(f) anti addition(反式加成)
(g) Markovnikov addition
(h) anti-Markovnikov addition(反马氏加成)
(i) peroxide effect(过氧化物效应)
(j) hydrogenation(加氢反应)
(k) hydration(加水反应)
(l) homogeneous catalysis(均相催化)
(m) heterogeneous catalysis(多相催化)
(n) halogenation(加卤素反应)
(o) halohydrin(卤化醇)
(p) hydroxylation(羟基化反应)
(q) epoxidation (环氧化反应)
(r) oxidative cleavage(氧化断裂)
(s) hydroboration (硼氢化反应)
(t) alpha elimination (消除反应)
(u) beta elimination
(v) oxymercuration-demercuration (羟汞化脱汞反应)
(w) carbene addition (卡宾加成)
(x) cationic polymerization (阳离子聚合)
(y) alkoxymercuration-demercuration (烷氧基汞化-脱汞反应)
(z) monomer (单体)
(aa) addition polymer (加成聚合)

9-30 Predict the major products of the following reactions, and give the structures of any intermediates. Include stereochemistry where appropriate.

(a) 

(b)

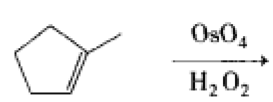
(c) 

(d) 

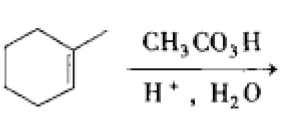
(e)

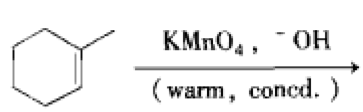
(f)

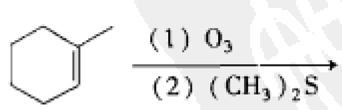
(g)

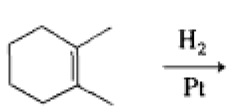
(h) 

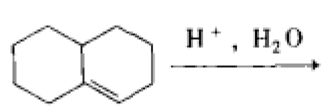
(i)

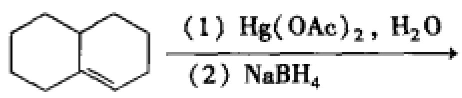
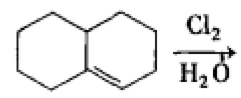
(j) 

(k) 

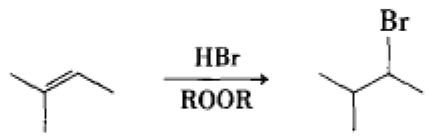
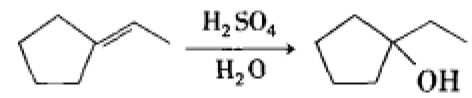
(l) 

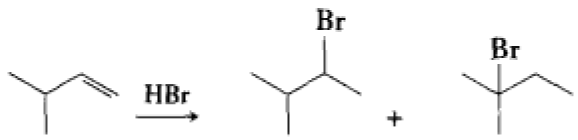
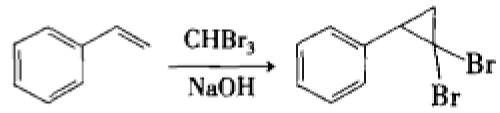
(m) 

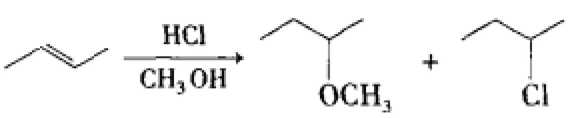
(n) 

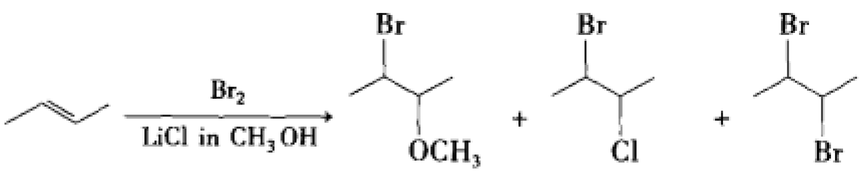
(o)  (p) 

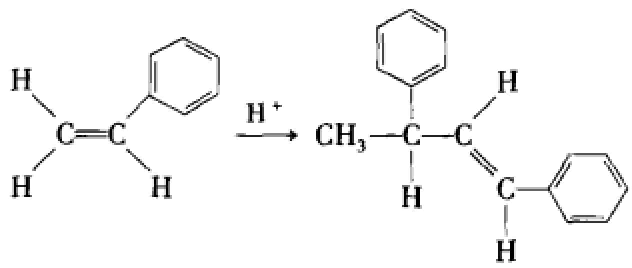
9−31 Propose mechanisms consistent with the following reactions.

(a)  (b) 

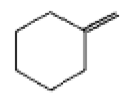
(c)  (d) 

(e) 

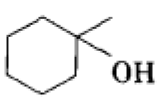
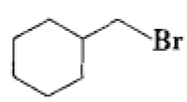
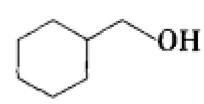
(f) 

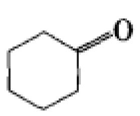
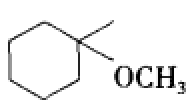
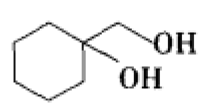
(g) 

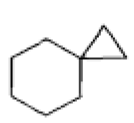
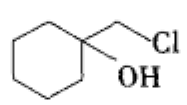
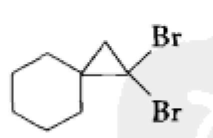
9−32 Show how you would synthesize each compound using methylenecyclohexane as your starting material.



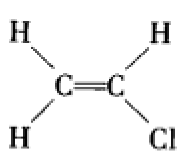
methylenecyclohexane

(a)  (b)  (c) 

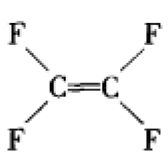
(d)  (e)  (f) 

(g)  (h)  (i) 

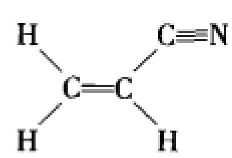
9−33 The structures of three monomers are shown. In each case, show the structure of the polymer that would result from polymerization of the monomer. Vinyl chloride is polymerized to "vinyl" plastics and PVC pipe. Tetrafluoroethylene polymerizes to Teflon®, used as non-stick coatings and PTFE valves and gaskets. Acrylonitrile is polymerized to Orlon®, used in sweaters and carpets.



vinyl chloride
(乙烯基氯)



tetrafluoroethylene
(四氟乙烯)



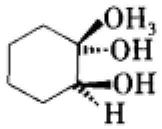
acrylonitrile
(丙烯腈)

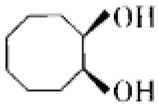
9−34 The cationic polymerization of isobutylene (2-methylpropene) is shown in Section 9−16A. Isobutylene is often polymerized

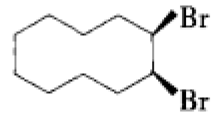
under free-radical conditions. Propose a mechanism for the free-radical polymerization of isobutylene.

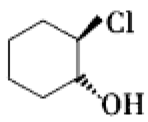
9−35 Draw a reaction-energy diagram for the propagation steps of the free-radical addition of HBr to isobutylene. Draw curves representing the reactions leading to both the Markovnikov and the anti-Markovnikov products. Compare the values of $\Delta G^{\ominus}$ and E_a for the rate-limiting steps, and explain why only one of these products is observed.

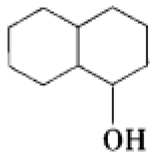
9−36 Show how you would make the following compounds from a suitable cyclic alkene.

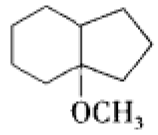
(a) 

(b) 

(c) 

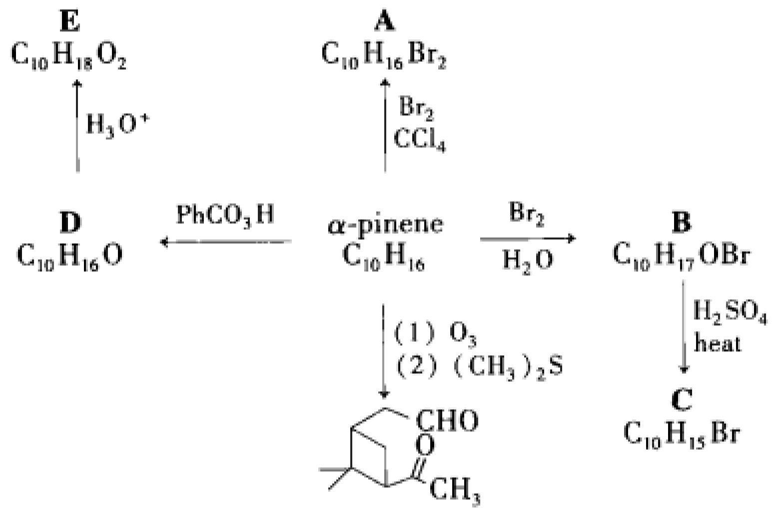
(d) 

(e) 

(f) 

9−37 Unknown **X**, C_5H_9Br, does not react with bromine or with dilute $KMnO_4$. Upon treatment with potassium *t*-butoxide, **X** gives only one product, **Y**, C_5H_8. Unlike **X**, **Y** decolorizes bromine and changes $KMnO_4$ from purple to brown. Catalytic hydrogenation of **Y** gives methylcyclobutane. Ozonolysis-reduction of **Y** gives dialdehyde **Z**, $C_5H_8O_2$. Propose consistent structures for **X**, **Y**, and **Z**. Is there any aspect of the structure of **X** that is still unknown?

9−38 One of the constituents of turpentine is α-pinene, formula $C_{10}H_{16}$. The following scheme (called a "road map") gives some reactions of α-pinene. Determine the structure of α-pinene and of the reaction products A through **E**.

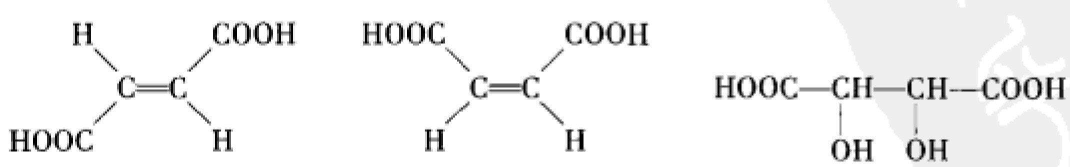


9−39 In contact with a platinum catalyst, an unknown alkene reacts with 3 equivalents of hydrogen gas to give 1-isopropyl-4-methylcyclohexane. When the unknown alkene is ozonized and reduced, the products are the following:

$$\mathrm{H{-}\overset{\overset{O}{\|}}{C}{-}H} \qquad \mathrm{H{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}CH_3} \qquad \mathrm{CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}H}$$

Deduce the structure of the unknown alkene.

9−40 The two butenedioic acids are called *fumaric acid* (trans) and *maleic acid* (cis). 2,3-Dihydroxybutanedioic acid is called *tartaric acid*.



fumaric acid (富马酸)　　maleic acid (马来酸)　　tartaric acid (酒石酸)

Show how you would convert

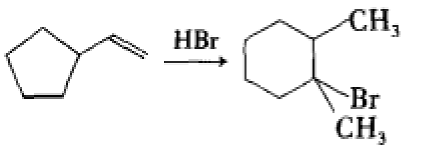
(**a**) fumaric acid to (±)-tartaric acid　　(**b**) fumaric acid to *meso*-tartaric acid

(**c**) maleic acid to (±)-tartaric acid　　(**d**) maleic acid to *meso*-tartaric acid.

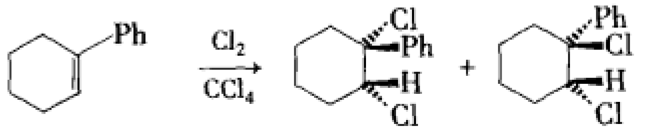
9−41 The compound BD_3 is a deuterated form of borane. Predict the product formed when 1-methylcyclohexene reacts with BD_3·

THF, followed by basic hydrogen peroxide.

9−42 A routine addition of HBr across the double bond of a vinylcyclopentane gave an unexpected rearranged product. Propose a mechanism for the formation of this product, and explain why the rearrangement occurs.



9−43 We have seen many examples where halogens add to alkenes with anti stereochemistry via the halonium ion mechanism. However, when 1-phenylcyclohexene reacts with chlorine in carbon tetrachloride, a mixture of the cis and trans isomers of the product is recovered. Propose a mechanism, and explain this lack of stereospecificity.



1-phenylcyclohexene *cis*- and *trans*-
1, 2-dichloro-1-phenylcyclohexane

Chapter 10
Alkynes

10-1 Introduction

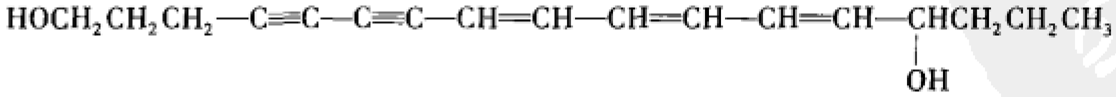
Alkynes are hydrocarbons that contain carbon-carbon triple bonds. Alkynes are also called **acetylenes** because they are derivatives of acetylene, the simplest alkyne.

$H{-}C{\equiv}C{-}H$	$CH_3CH_2{-}C{\equiv}C{-}H$	$CH_3{-}C{\equiv}C{-}CH_3$
acetylene	ethylacetylene	dimethylacetylene
ethyne（乙炔）	1-butyne（1－丁炔）	2-butyne（2－丁炔）

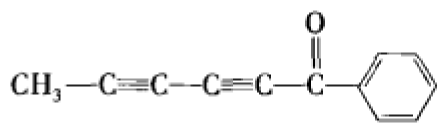
The chemistry of the carbon-carbon triple bond is similar to that of the double bond. In this chapter, we see that alkynes undergo most of the same reactions as alkenes, especially the additions and the oxidations. We also consider reactions that are specific to alkynes: some that depend on the unique characteristics of the $C{\equiv}C$ triple bond, and others that depend on the unusual acidity of the acetylenic C—H bond.

A triple bond gives an alkyne four fewer hydrogens than the corresponding alkane. Its molecular formula is like that of a molecule with two double bonds: C_nH_{2n-2}. Therefore, the triple bond contributes two elements of unsaturation (eu).

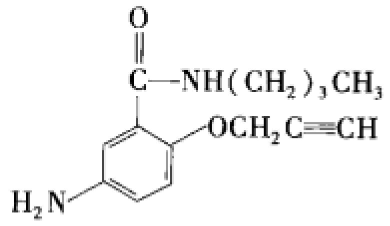
Alkynes are not as common in nature as alkenes, but some plants do use alkynes to protect themselves against disease or predators. Cicutoxin is a toxic compound found in water hemlock, and capillin protects a plant against fungal diseases. The alkyne functional group is not common in drugs, but parsalmide is used as an analgesic, and ethynyl estradiol (a synthetic female hormone) is a common ingredient in birth control pills. Dynemicin A is an antibacterial compound that is being tested as an antitumor agent.



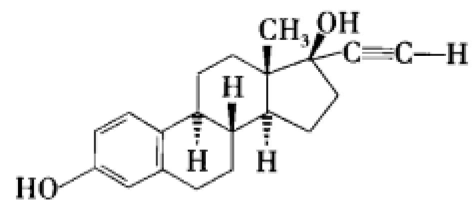
cicutoxin（毒芹素）



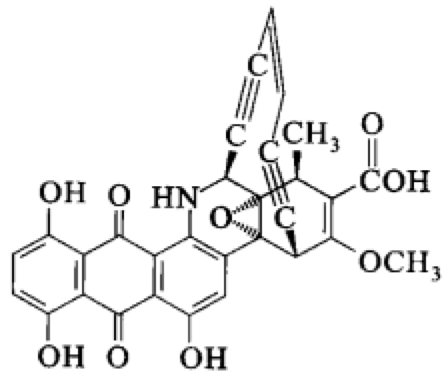
capillin（毛蒿素）



parsalmide



ethynyl estradiol
（乙炔基雌甾二醇）



dynemicin A

10−2 Physical Properties of Alkynes

The physical properties of alkynes (Table 10−1) are similar to those of alkanes and alkenes of similar molecular weights. Alkynes are relatively nonpolar and nearly insoluble in water. They are quite soluble in most organic solvents, including acetone, ether, methylene chloride, chloroform, and alcohols. Many alkynes have characteristic, mildly offensive odors. Acetylene, propyne, and the butynes are gases at room temperature, just like the corresponding alkanes and alkenes. In fact, the boiling points of alkynes are nearly the same as those of alkanes and alkenes with similar carbon skeletons.

TABLE 10−1 Physical Properties of Selected Alkynes

Name	Chinese Name	Structure	mp/℃	bp/℃	Density/(g·cm^{-3})
ethyne (acetylene)	乙炔	$H—C{\equiv}C—H$	-82	-84	0.62
propyne	丙炔	$H—C{\equiv}C—CH_3$	-101	-23	0.67
1-butyne	1−丁炔	$H—C{\equiv}C—CH_2CH_3$	-126	8	0.67
2-butyne	2−丁炔	$CH_3—C{\equiv}C—CH_3$	-32	27	0.69
1-pentyne	1−戊炔	$H—C{\equiv}C—CH_2CH_2CH_3$	-90	40	0.70
2-pentyne	2−戊炔	$CH_3—C{\equiv}C—CH_2CH_3$	-101	55	0.71
3-methyl-1-butyne	3−甲基−1−丁炔	$CH_3—CH(CH_3)—C{\equiv}C—H$		28	0.67
1-hexyne	1−己炔	$H—C{\equiv}C—(CH_2)_3—CH_3$	-132	71	0.72
2-hexyne	2−己炔	$CH_3—C{\equiv}C—CH_2CH_2CH_3$	-90	84	0.73
3-hexyne	3−己炔	$CH_3CH_2—C{\equiv}C—CH_2CH_3$	-101	82	0.73
3,3-dimethyl-1-butyne	3,3−二甲基−1−丁炔	$(CH_3)_3C—C{\equiv}C—H$	-81	38	0.67
1-heptyne	1−庚炔	$H—C{\equiv}C—(CH_2)_4CH_3$	-81	100	0.73
1-octyne	1−辛炔	$H—C{\equiv}C—(CH_2)_5CH_3$	-79	125	0.75
1-nonyne	1−壬炔	$H—C{\equiv}C—(CH_2)_6CH_3$	-50	151	0.76
1-decyne	1−癸炔	$H—C{\equiv}C—(CH_2)_7CH_3$	-36	174	0.77

10−3 Commercial Importance of Alkynes

10−3A Uses of Acetylene and Methylacetylene

Acetylene is by far the most important commercial alkyne. Acetylene is an important industrial feedstock, but its largest use is as the fuel for the oxyacetylene welding torch. Acetylene is a colorless, foul-smelling gas that burns

in air with a yellow, sooty flame. When the flame is supplied with pure oxygen, however, the color turns to light blue, and flame temperature increases dramatically. A comparison of the heat of combustion for acetylene with those of ethene and ethane shows why this gas makes an excellent fuel for a high-temperature flame.

$$CH_3CH_3 + \frac{7}{2}O_2 \longrightarrow 2CO_2 + 3H_2O \qquad \Delta H^\ominus = -1\,561 \text{ kJ}$$

$-1\,561$ kJ divided by 5 mol of products = -312 kJ/mol of products

$$H_2C{=}CH_2 + 3O_2 \longrightarrow 2CO_2 + 2H_2O \qquad \Delta H^\ominus = -1\,410 \text{ kJ}$$

$-1\,410$ kJ divided by 4 mol of products = -352 kJ/mol of products

$$HC{\equiv}CH + \frac{5}{2}O_2 \longrightarrow 2CO_2 + 1H_2O \qquad \Delta H^\ominus = -1\,326 \text{ kJ}$$

$-1\,326$ kJ divided by 3 mol of products = -442 kJ/mol of products

If we were simply heating a house by burning one of these fuels, we might choose ethane as our fuel because it produces the most heat per mole of gas consumed. In the welding torch, we want the highest possible *temperature* of the gaseous products. The heat of reaction must raise the temperature of the products to the flame temperature. Roughly speaking, the increase in temperature of the products is proportional to the heat given off *per mole of products* formed. This rise in temperature is largest with acetylene, which gives off the most heat per mole of products. The oxyacetylene flame reaches temperatures as high as 2 800 ℃.

When acetylene was first used for welding, it was considered a dangerous, explosive gas. Acetylene is thermodynamically unstable. When the compressed gas is subjected to thermal or mechanical shock, it decomposes to its elements, releasing 234 kJ of energy per mole. This initial decomposition often splits the container, allowing the products (hydrogen and finely divided carbon) to burn in the air.

$$H{-}C{\equiv}C{-}H \longrightarrow 2C + H_2 \qquad \Delta H^\ominus = -234 \text{ kJ/mol}$$

$$2C + H_2 \xrightarrow{\frac{5}{2}O_2} 2CO_2 + H_2O \qquad \Delta H^\ominus = -1\,090 \text{ kJ/mol}$$

Acetylene is safely stored and handled in cylinders that are filled with crushed firebrick wet with acetone. Acetylene dissolves freely in acetone, and the dissolved gas is not so prone to decomposition. Firebrick helps to control the decomposition by minimizing the free volume of the cylinder, cooling and controlling any decomposition before it gets out of control.

Methylacetylene also is used in welding torches. Methylacetylene does not decompose as easily as acetylene, and it burns better in air (as opposed to pure oxygen). Methylacetylene is well suited for household soldering and brazing that requires higher temperatures than propane torches can reach. The industrial synthesis of methylacetylene gives a mixture with its isomer, propadiene (allene). This mixture is sold commercially under the name MAPP® gas (*M*ethyl*A*cetylene-*P*ro*P*adiene).

$CH_3{-}C{\equiv}C{-}H$	$H_2C{=}C{=}CH_2$
methylacetylene (甲基乙炔)	propadiene (allene) (丙二烯)

10-3B Manufacture of Acetylene

Acetylene, one of the cheapest organic chemicals, is made from coal or from natural gas. The synthesis from coal involves heating lime and coke (roasted coal) in an electric furnace to produce calcium carbide. Addition of water to calcium carbide produces acetylene and hydrated lime.

$$\underset{\text{coke}}{3C} + \underset{\text{lime}}{CaO} \xrightarrow{\text{electric furnace, 2 500 ℃}} \underset{\text{calcium carbide (碳化钙)}}{CaC_2 + CO}$$

$$CaC_2 + 2H_2O \longrightarrow \underset{\text{acetylene}}{H{-}C{\equiv}C{-}H} + \underset{\text{hydrated lime (熟石灰)}}{Ca(OH)_2}$$

This second reaction once served as a light source in coal mines until battery-powered lights became available. A miner's lamp works by allowing water to drip slowly onto some calcium carbide. Acetylene is generated, feeding a small flame where the gas burns in air with a yellow flickering light. Unfortunately, this flame ignites the methane gas commonly found in coal seams, causing explosions. Battery-powered miner's lamps provide better light and reduce the danger of methane explosions.

The synthesis of acetylene from natural gas is a simple process. Natural gas consists mostly of methane, which forms acetylene when it is heated for a very short period of time.

$$2CH_4 \xrightarrow[0.01\ \text{s}]{1\,500\ ℃} H{-}C{\equiv}C{-}H + 3H_2$$

Although this reaction is endothermic, there are twice as many moles of products as reactants. The increase in the number of moles results in an increase in entropy, and the $(-T\Delta S)$ term in the free energy $(\Delta G = \Delta H - T\Delta S)$ predominates at this high temperature.

PROBLEM 10-1

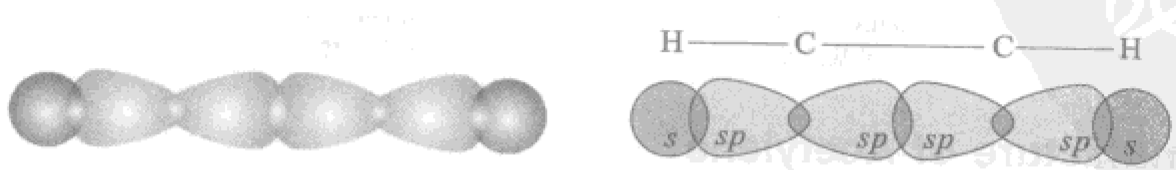
What reaction would acetylene likely undergo if it were kept at 1 500 ℃ for too long?

10-4 Electronic Structure of Alkynes

In Section 2-4, we studied the electronic structure of a triple bond. Let's review this structure, using acetylene as the example. The Lewis structure of acetylene shows three pairs of electrons in the region between the carbon nuclei:

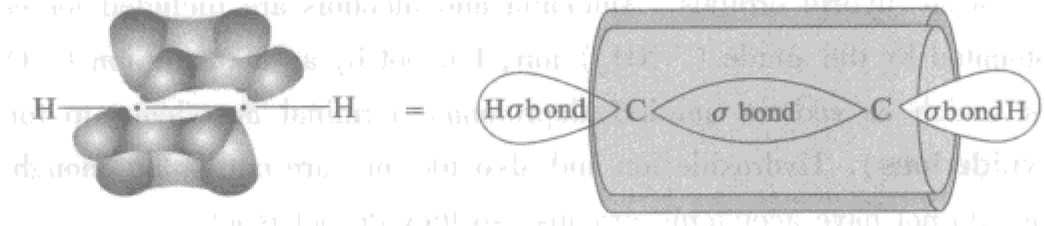
$$H{:}C{:::}C{:}H$$

Each carbon atom is bonded to two other atoms, and there are no nonbonding valence electrons. Each carbon atom needs two hybrid orbitals to form the sigma bond framework. Hybridization of the *s* orbital with one *p* orbital gives two hybrid orbitals, directed 180° apart, for each carbon atom. Overlap of these *sp* hybrid orbitals with each other and with the hydrogen *s* orbitals gives the sigma bond framework. Experimental results have confirmed this linear (180°) structure.



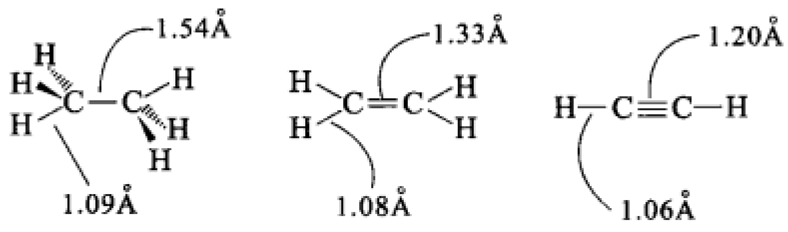
Two pi bonds result from overlap of the two remaining unhybridized *p* orbitals on each carbon atom. These orbitals overlap at right angles to each other, forming one pi bond with electron density above and below the C—C sigma bond, and the other with electron density in front and in back of the sigma bond. The shape of these pi

bonds is such that they blend to form a cylinder of electron density encircling the sigma bond between the two carbon atoms.



overlap of p orbitals — cylinder of electron density

The carbon-carbon bond length in acetylene is 1.20 Å, and each carbon-hydrogen bond is 1.06 Å. Both bonds are shorter than the corresponding bonds in ethane and in ethene.



The triple bond is relatively short because of the attractive overlap of three bonding pairs of electrons and the high *s* **character** of the *sp* hybrid orbitals. The *sp* hybrid orbitals are about one-half *s* character (as opposed to one-third *s* character of sp^2 hybrids and one-fourth of sp^3 hybrids), using more of the closer, tightly held *s* orbitals. The *sp* hybrid orbitals also account for the slightly shorter C—H bonds in acetylene compared with ethylene.

10-5 Acidity of Alkynes; Formation of Acetylide Ions

Terminal alkynes are much more acidic than other hydrocarbons. Removal of an acetylenic proton forms an acetylide ion, which plays a central role in alkyne chemistry.

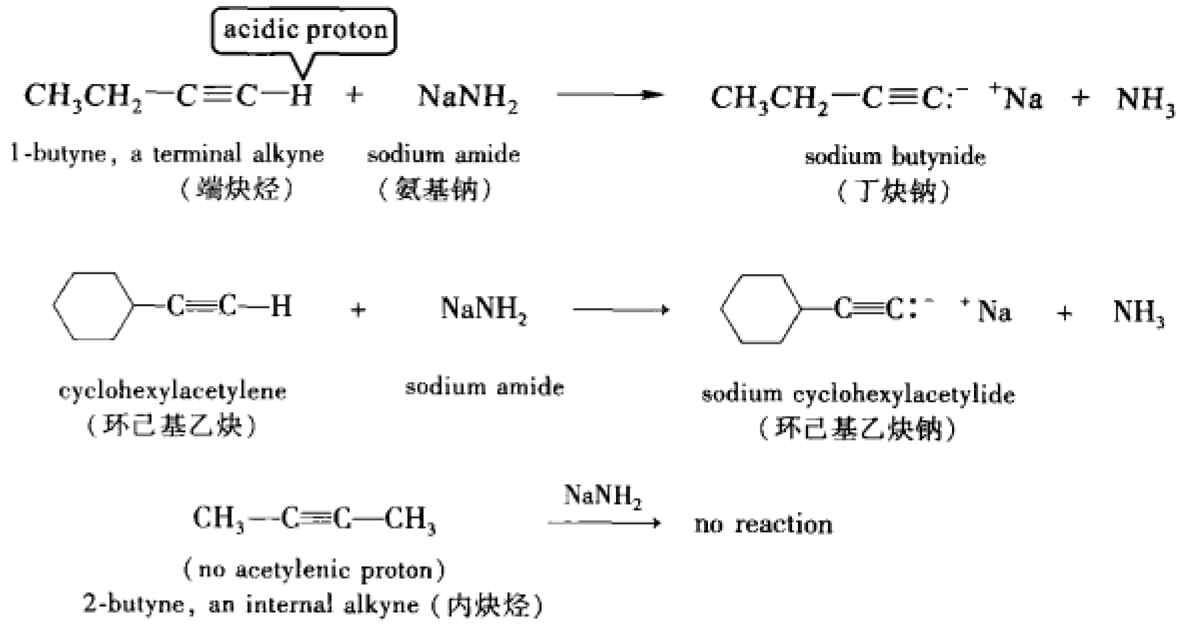
The acidity of an acetylenic hydrogen stems from the nature of the *sp* hybrid ≡C—H bond. Table 10-2 shows how the acidity of a C—H bond varies with its hybridization, increasing with the increasing *s* character of the orbitals: $sp^3 < sp^2 < sp$. (Remember that a *smaller* value of pK_a corresponds to a stronger acid.) The acetylenic proton is about 10^{19} times as acidic as a vinyl proton.

TABLE 10-2 Physical Properties of Selected Alkynes

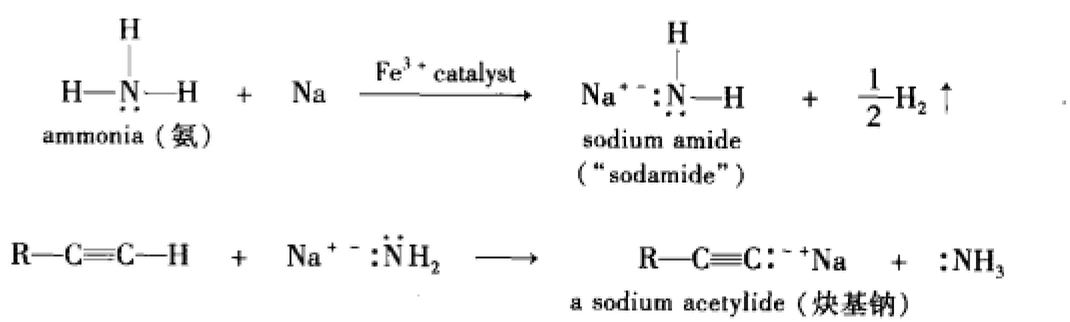
Compound	Conjugate Base	Hybridization	*s* Character	pK_a	
H_3C-CH_3	$H_3C-CH_2^-$	sp^3	25%	50	weakest acid
$H_2C=CH_2$	$H_2C=CH^-$	sp^2	33%	44	
$:NH_3$	$:\ddot{N}H_2^-$	(ammonia)		35	
H—C≡C—H	H—C≡C:⁻	sp	50%	25	
R—OH	R—$\ddot{\text{O}}$:⁻	(alcohols)		16-18	stronger acid

Abstraction of an acetylenic proton gives a carbanion that has the lone pair of electrons in the *sp* hybrid orbital. Electrons in this orbital are close to the nucleus, and there is less charge separation than in carbanions with the lone pair in sp^2 or sp^3 hybrid orbitals. Ammonia and alcohols are included for comparison; note that acetylene can be deprotonated by the amide ($^-NH_2$) ion, but not by an alkoxide ion (^-OR).

Very strong bases (such as sodium amide) deprotonate terminal acetylenes to form carbanions called **acetylide ions** (or **alkynide ions**). Hydroxide ion and alkoxide ions are not strong enough bases to deprotonate alkynes. Internal alkynes do not have acetylenic protons, so they do not react.



Sodium amide ($Na^{+}\ ^{-}:\ddot{N}H_2$) is frequently used as the base in forming acetylide salts. The amide ion ($^-NH_2$) is the conjugate base of ammonia, a compound that is itself a base. Ammonia is also a very weak acid, however, with $K_a = 10^{-35}$ ($pK_a = 35$). One of its hydrogens can be reduced by sodium metal to give the sodium salt of the amide ion, a very strong conjugate base.



Acetylide ions are strong nucleophiles. In fact, one of the best methods for synthesizing substituted alkynes is a nucleophilic attack by an acetylide ion on an unhindered alkyl halide. We consider this displacement reaction in detail in Section 10-6A.

PROBLEM 10-2

The boiling points of 1-hexene (64 ℃) and 1-hexyne (71 ℃) are sufficiently close that it is difficult to achieve a clean separation by distillation. Show how you might use the acidity of 1-hexyne to remove the last trace of it from a sample of 1-hexene.

PROBLEM 10-3

Predict the products of the following acid-base reactions, or indicate if no significant reaction would take place.

(a) $H—C\equiv C—H + NaNH_2$
(b) $H—C\equiv C—H + CH_3Li$
(c) $H—C\equiv C—H + NaOCH_3$
(d) $H—C\equiv C—H + NaOH$
(e) $H—C\equiv C:^{-}\,{}^{+}Na + CH_3OH$
(f) $H—C\equiv C:^{-}\,{}^{+}Na + H_2O$
(g) $H—C\equiv C:^{-}\,{}^{+}Na + H_2C{=}CH_2$
(h) $H_2C{=}CH_2 + NaNH_2$
(i) $CH_3OH + NaNH_2$

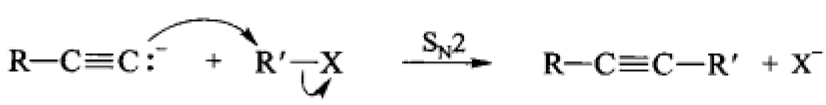
10-6 Synthesis of Alkynes from Acetylides

Two different approaches are commonly used for the synthesis of alkynes. In the first, an appropriate electrophile undergoes nucleophilic attack by an acetylide ion. The electrophile may be an unhindered primary alkyl halide (undergoes S_N2), or it may be a carbonyl compound (undergoes addition to give an alcohol). Either reaction joins two fragments and gives a product with a lengthened carbon skeleton. This approach is used in many laboratory syntheses of alkynes.

The second approach forms the triple bond by a double dehydrohalogenation of a dihalide. This reaction does not enlarge the carbon skeleton. Isomerization of the triple bond may occur (see Section 10-7), so dehydrohalogenation is useful only when the desired product has the triple bond in a thermodynamically favored position.

10-6A Alkylation of Acetylide Ions

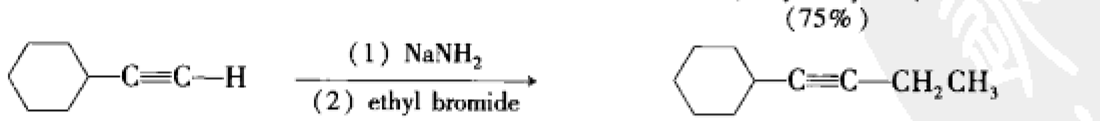
An acetylide ion is a strong base and a powerful nucleophile. It can displace a halide ion from a suitable substrate, giving a substituted acetylene.



(R'—X must be a primary alkyl halide)

If this S_N2 reaction is to produce a good yield, the alkyl halide must be an excellent S_N2 substrate: It must be primary, with no bulky substituents or branches close to the reaction center. In the following examples, acetylide ions displace primary halides to form elongated alkynes.

$$\underset{\text{sodium acetylide (乙炔钠)}}{H—C\equiv C:^{-}\,{}^{+}Na} + \underset{\text{1-bromobutane}}{CH_3CH_2CH_2CH_2—Br} \longrightarrow \underset{\text{1-hexyne (butylacetylene) (75\%)}}{H—C\equiv C—CH_2CH_2CH_2CH_3} + NaBr$$



ethynylcyclohexane (cyclohexylacetylene) → 1-cyclohexyl-1-butyne (1-环己基-1-丁炔) (ethylcyclohexylacetylene) (70%)

If the back-side approach is hindered, the acetylide ion may abstract a proton, giving elimination by the E2 mechanism.

$$\underset{\text{butynide ion (炔基负离子)}}{CH_3CH_2—C\equiv C:^{-}} + \underset{\text{isopropyl bromide (异丙基溴)}}{H_3C—\overset{Br}{\overset{|}{C}}H—CH_3} \xrightarrow{E2} \underset{\text{butyne}}{CH_3CH_2—C\equiv C—H} + \underset{\text{propene}}{H_2C{=}CH—CH_3} + Br^{-}$$

PROBLEM 10-4

Show how you might synthesize the following compounds, using acetylene and any suitable alkyl halides as your starting materials. If the compound given cannot be synthesized by this method, explain why.

(a) 1-hexyne (b) 2-hexyne

(c) 3-hexyne (d) 4-methyl-2-hexyne

(e) 5-methyl-2-hexyne (f) cyclodecyne

10-6B Addition of Acetylide Ions to Carbonyl Groups

Like other carbanions, acetylide ions are strong nucleophiles and strong bases. In addition to displacing halide ions in S_N2 reactions, they can add to carbonyl (C=O) groups. Figure 10-1 shows the structure of the carbonyl group. Because oxygen is more electronegative than carbon, the C=O double bond is polarized. The oxygen atom has a partial negative charge balanced by an equal amount of positive charge on the carbon atom.

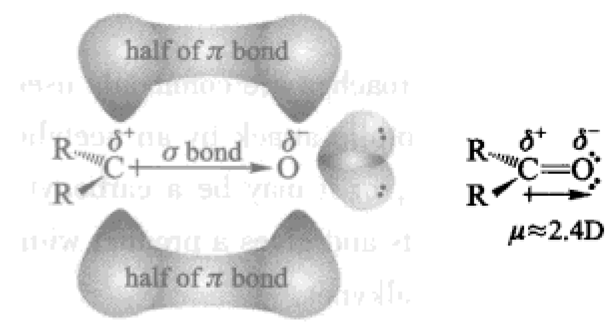
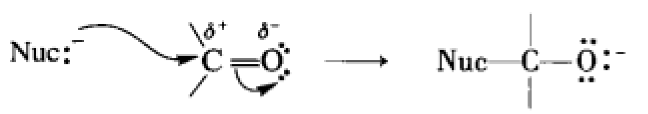
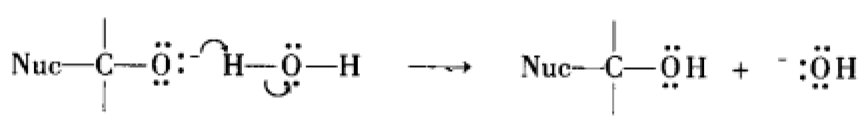


Figure 10-1 The C=O double bond of a carbonyl group resembles the C=C double bond of an alkene; however, the carbonyl double bond is strongly polarized. The oxygen atom bears a partial negative charge, and the carbon atom bears a partial positive charge.

The positively charged carbon is electrophilic; attack by a nucleophile places a negative charge on the electronegative oxygen atom.

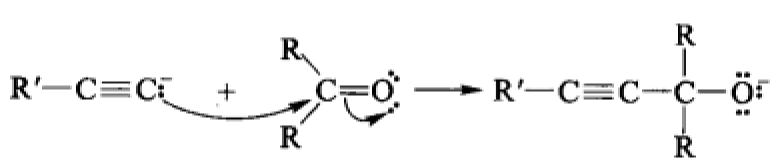


The product of this nucleophilic attack is an alkoxide ion, a strong base. (An **alkoxide ion** is the conjugate base of an alcohol, a weak acid.) Addition of water or a dilute acid protonates the alkoxide to give the alcohol.

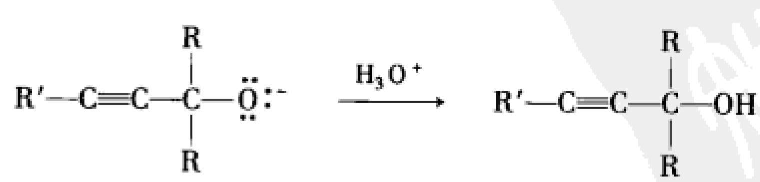


alkoxide (or H_3O^+)
(烷氧基负离子)

An acetylide ion can serve as the nucleophile in this addition to a carbonyl group. The acetylide ion adds to the carbonyl group to form an alkoxide ion. Addition of dilute acid (in a separate step) protonates the alkoxide to give the alcohol.

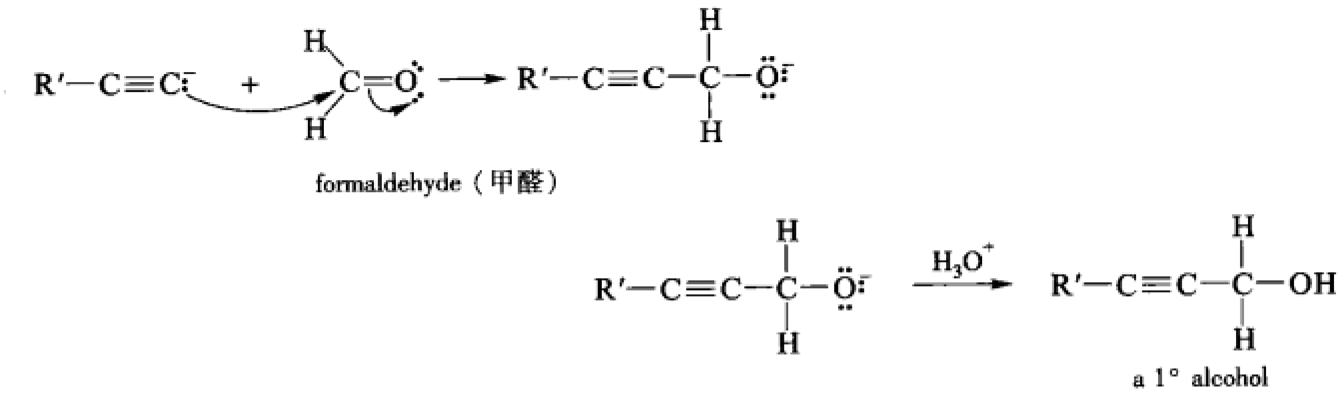


acetylide (炔负离子) aldehyde or ketone



an acetylenic alcohol
(取代的炔丙醇)

An acetylide adds to formaldehyde ($H_2C=O$) to give (after the protonation step) a primary alcohol with one more carbon atom than there was in the acetylide.

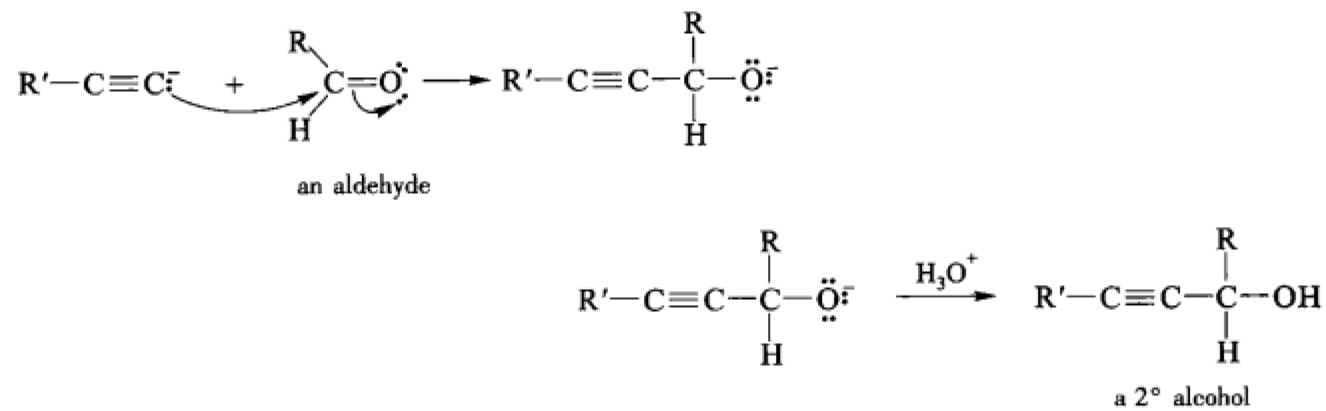


Example

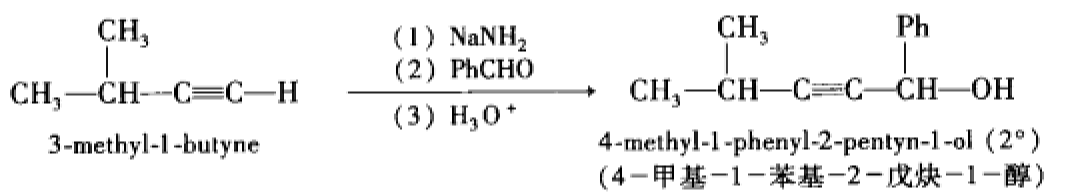
$$CH_3—C≡C—H \xrightarrow[(3)\ H_3O^+]{(1)\ NaNH_2 \quad (2)\ H_2C=O} CH_3—C≡C—CH_2—OH$$

propyne → 2-butyn-1-ol (1°)(2-丁炔-1-醇)

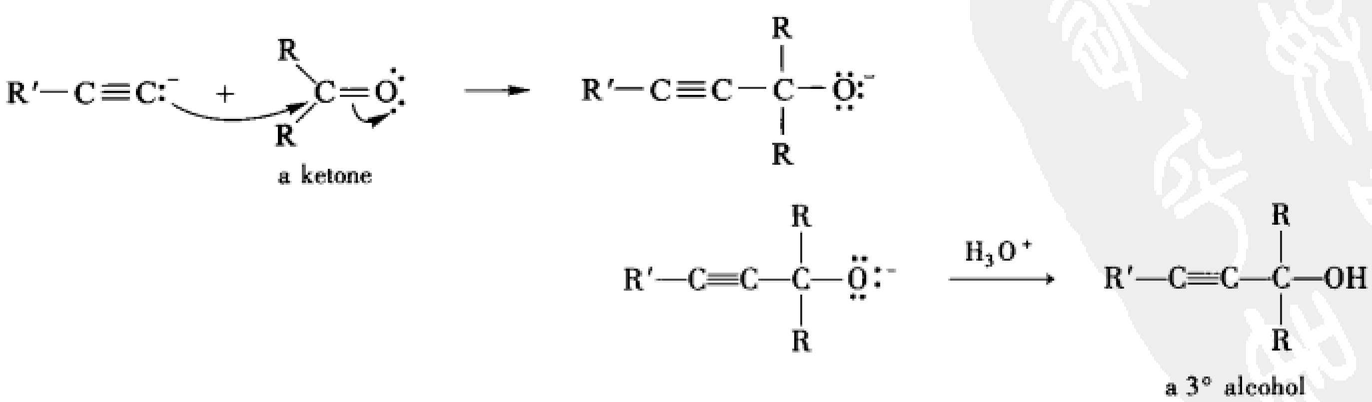
An acetylide adds to an aldehyde to give, after protonation, a secondary alcohol. The two groups of the secondary alcohol are the acetylide and the alkyl group that was bonded to the carbonyl group of the aldehyde.



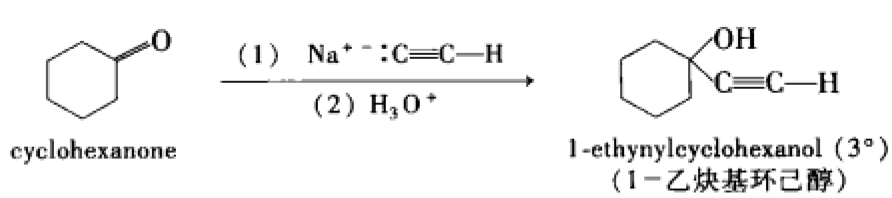
Example



A ketone has two alkyl groups bonded to its carbonyl carbon atom. Addition of an acetylide, followed by protonation, gives a tertiary alcohol. The three alkyl groups bonded to the carbinol carbon atom (the carbon bearing the —OH group) are the acetylide and the two alkyl groups originally bonded to the carbonyl group in the ketone.

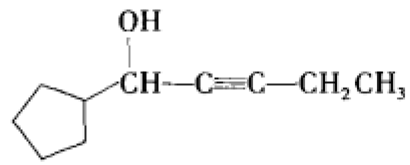


Example



SOLVED PROBLEM 10-1

Show how you would synthesize the following compound, beginning with acetylene and any necessary additional reagents.

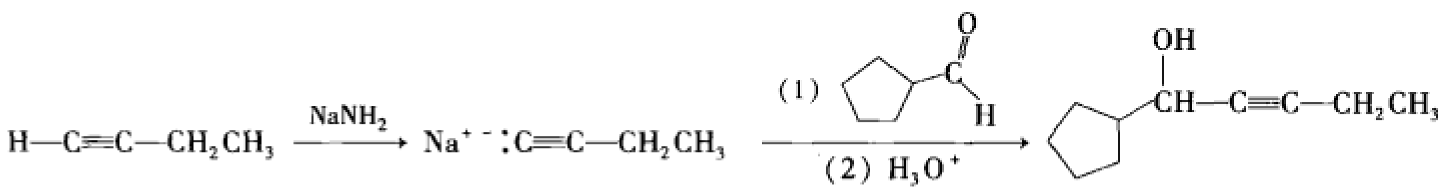


SOLUTION

We need to add two groups to acetylene: an ethyl group and a six-carbon aldehyde (to form the secondary alcohol). If we formed the alcohol group first, the weakly acidic —OH group would interfere with the alkylation by the ethyl group. Therefore, we should add the less reactive ethyl group first, and add the alcohol group later in the synthesis.

$$H-C\equiv C-H \xrightarrow[(2)\ CH_3CH_2Br]{(1)\ NaNH_2} H-C\equiv C-CH_2CH_3$$

The ethyl group is not acidic, and it does not interfere with the addition of the second group:



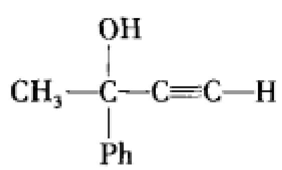
PROBLEM 10-5

Show how you would synthesize each compound, beginning with acetylene and any necessary additional reagents.

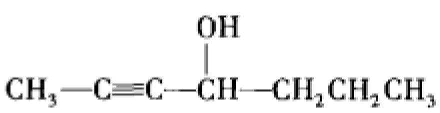
(a) 2-propyn-1-ol (propargyl alcohol)

$$H-C\equiv C-CH_2OH$$

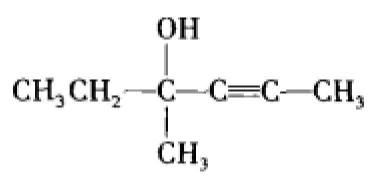
(b) 2-phenyl-3-butyn-2-ol



(c) 2-heptyn-4-ol

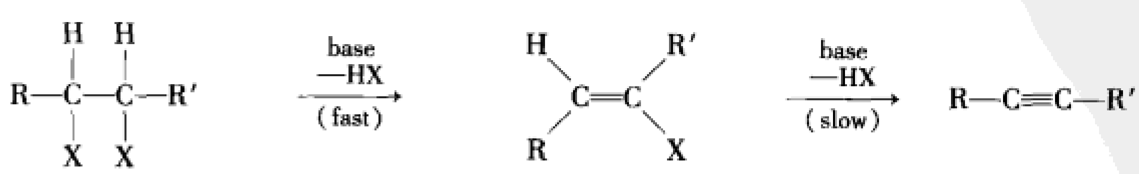


(d) 3-methyl-4-hexyn-3-ol

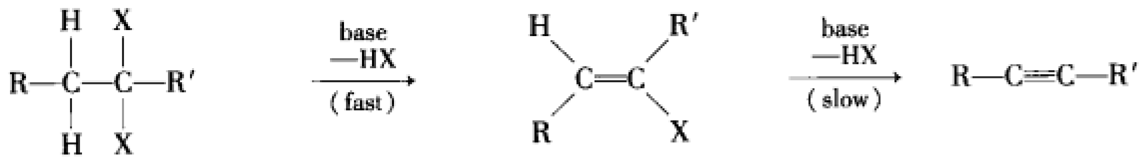


10-7 Synthesis of Alkynes by Elimination Reactions

In some cases, we can generate a carbon-carbon triple bond by eliminating two molecules of HX from a dihalide. Dehydrohalogenation of a *geminal* or *vicinal* dihalide gives a vinyl halide. Under strongly basic conditions, a second dehydrohalogenation may occur to form an alkyne.



a vicinal dihalide (邻二卤代物) vinyl halide (乙烯基卤代物) alkyne



a geminal dihalide (偕二卤代物)　　vinyl halide　　alkyne

Conditions for Elimination We have already seen (Section 8−7A) many examples of dehydrohalogenation of alkyl halides. The second step is new, however, because it involves dehydrohalogenation of a vinyl halide to give an alkyne. This second dehydrohalogenation occurs only under extremely basic conditions. For example, fused (molten) KOH or alcoholic KOH in a sealed tube, usually heated to temperatures close to 200 ℃. Sodium amide is also used for the double dehydrohalogenation. Since the amide ion ($^{-}:\ddot{N}H_2$) is a much stronger base than hydroxide, the amide reaction takes place at a lower temperature. The following reactions are carefully chosen to form products that do not rearrange (see below).

$$CH_3-CH_2-\underset{}{\overset{Br}{\overset{|}{C}}}H-\overset{Br}{\overset{|}{C}}H-CH_3 \xrightarrow[200\ ℃]{KOH(fused)} CH_3-CH_2-C\equiv C-CH_3$$

2,3-dibromopentane　　2-pentyne (45%)

$$CH_3-CH_2-CH_2-CH_2-CHCl_2 \xrightarrow[(2)\ H_2O]{(1)\ NaNH_2,\ 150\ ℃} CH_3-CH_2-CH_2-C\equiv C-H$$

1,1-dichloropentane　　1-pentyne (55%)

Base-Catalyzed Rearrangements Unfortunately, the double dehydrohalogenation is limited by the severe conditions. Any functional groups that are sensitive to strong bases cannot survive; also, the alkyne products may rearrange under these extremely basic conditions. Figure 10−2 shows how the loss of protons at one carbon atom and their replacement elsewhere leads to isomerization of the triple bond. This ability to isomerize implies that all the possible triple-bond isomers will equilibrate, and the most stable isomer will predominate. The most stable alkyne isomer is usually the internal alkyne or a mixture of internal alkynes.

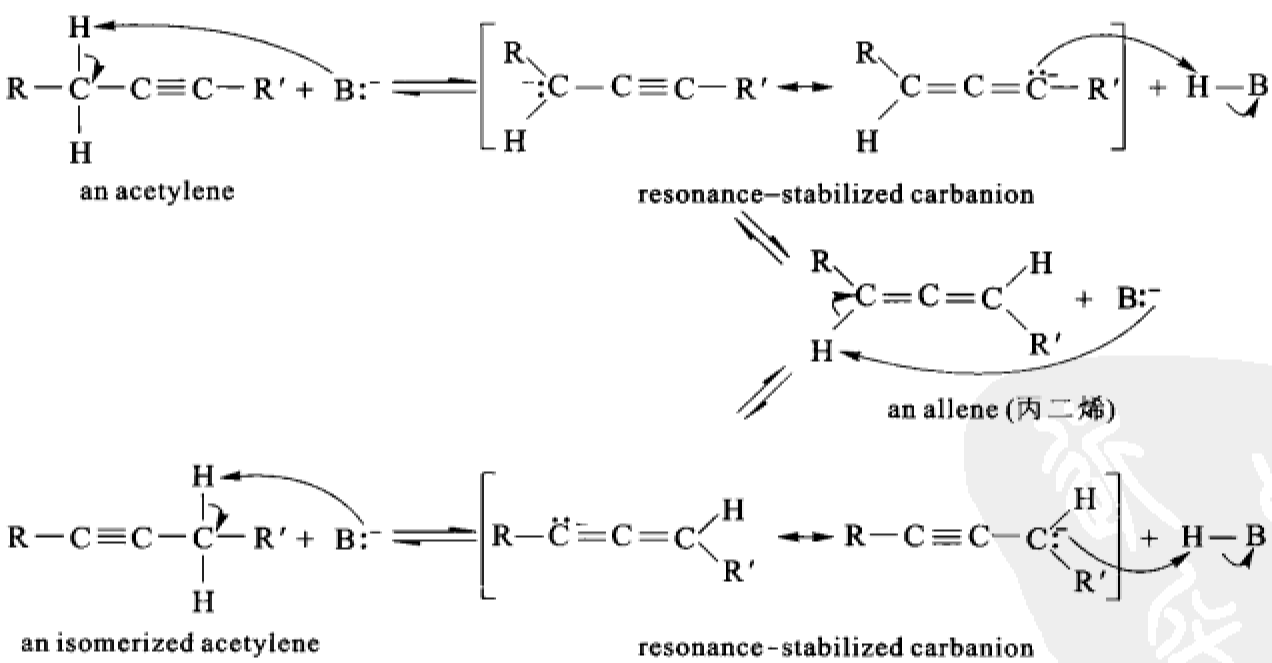
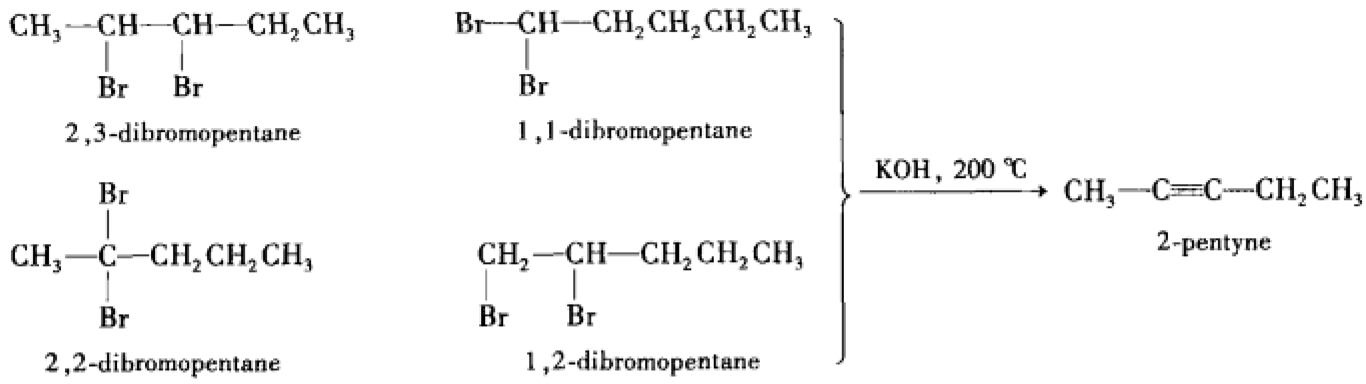


Figure 10−2 Under extremely basic conditions, an acetylenic triple bond can migrate along the carbon chain by repeated deprotonation and reprotonation.

Any of several isomers of dibromopentane give mostly 2-pentyne on dehydrohalogenation with fused KOH at 200 ℃. In each case, the alkyne initially formed rearranges to the most stable isomer, 2-pentyne.



PROBLEM 10-6

Give a mechanism to show how 1,1-dibromopentane reacts with fused KOH at 200 ℃ to give 2-pentyne.

Isomerization also results when sodium amide is used as the base in the double dehydrohalogenation. All possible triple-bond isomers are formed, but sodium amide is such a strong base that it deprotonates the terminal acetylene, removing it from the equilibrium. The acetylide ion becomes the favored product. When water is added to quench the reaction, the acetylide ion is protonated to give the terminal alkyne.

$$\underset{\text{one component of the mixture}}{R{-}C{\equiv}C{-}H} + {}^{-}\!:\ddot{N}H_2 \rightleftharpoons \underset{\text{acetylide ion (炔基负离子) (major component)}}{R{-}C{\equiv}C:^{-}} + :NH_3 \xrightarrow{H_2O} \underset{\text{major product}}{R{-}C{\equiv}C{-}H}$$

$$\underset{\text{2-octyne}}{CH_3(CH_2)_4{-}C{\equiv}C{-}CH_3} \xrightarrow[(2)\ H_2O]{(1)\ NaNH_2,\ 150\ ℃} \underset{\text{1-octyne (80\%)}}{CH_3(CH_2)_4{-}CH_2{-}C{\equiv}C{-}H}$$

PROBLEM 10-7

(a) Propose a mechanism to show how 2-pentyne reacts with sodium amide to give 1-pentyne.

(b) Explain how this reaction converts a more stable isomer (2-pentyne) to a less stable isomer (1-pentyne).

(c) How would you accomplish the opposite reaction, converting 1-pentyne into 2-pentyne?

PROBLEM 10-8

Show which of the following compounds could be synthesized in good yield by a double dehydrohalogenation from a dihalide. In each case.

1. Show which base you would use (KOH or $NaNH_2$).
2. Show how your starting material might be synthesized from an alkene.

(a) 2-butyne (b) 1-octyne

(c) 2-octyne (d) cyclodecyne

10-8 Addition Reactions of Alkynes

We have already discussed some of the most important reactions of alkynes. The nucleophilic attack of acetylide

ions on electrophiles, for example, is one of the best methods for making more complicated alkynes (Section 10−6). Now we consider reactions that involve transformations of the carbon-carbon triple bond itself.

Many of the reactions of alkynes are similar to the corresponding reactions of alkenes because both involve pi bonds between two carbon atoms. Like the pi bond of an alkene, the pi bonds of an alkyne are electron-rich, and they readily undergo addition reactions. Table 10−3 shows how the energy differences between the kinds of carbon-carbon bonds can be used to estimate how much energy it takes to break a particular bond. The bond energy of the alkyne triple bond is only about 226 kJ more than the bond energy of an alkene double bond. This is the energy needed to break one of the pi bonds of an alkyne.

Reagents add across the triple bonds of alkynes just as they add across the double bonds of alkenes. In effect, this reaction converts a pi bond and a sigma bond into two sigma bonds. Since sigma bonds are generally stronger than pi bonds, the reaction is usually exothermic. Alkynes have two pi bonds, so up to two molecules can add across the triple bond, depending on the reagents and the conditions.

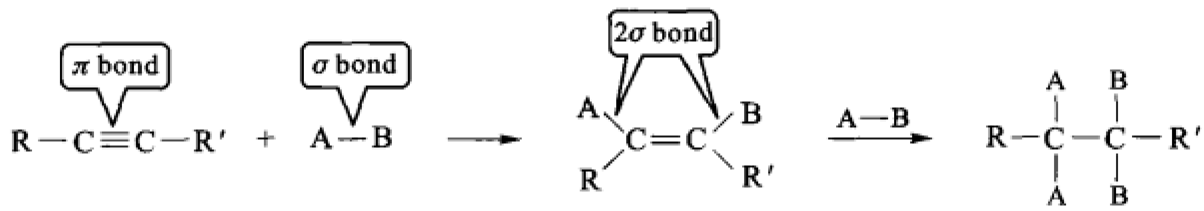


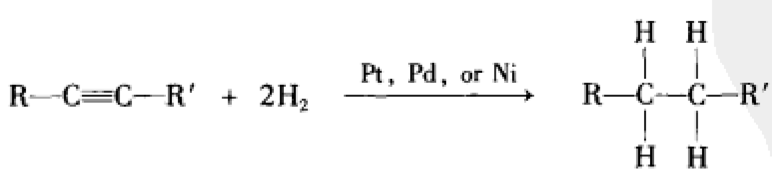
TABLE 10−3 Approximate Bond Energies of Carbon-Carbon Bonds

Bond	Total Energy	Class of Bond	Approximate Energy
C—C	347 kJ	alkane sigma bond	347 kJ
C=C	611 kJ	alkene pi bond	264 kJ
C≡C	837 kJ	second alkyne pi bond	226 kJ

We must consider the possibility of a double addition whenever a reagent adds across the triple bond of an alkyne. Some conditions may allow the reaction to stop after a single addition, while other conditions give double addition.

10−8A Catalytic Hydrogenation to Alkanes

In the presence of a suitable catalyst, hydrogen adds to an alkyne, reducing it to an alkane. For example, when either of the butyne isomers reacts with hydrogen and a platinum catalyst, the product is *n*-butane. Platinum, palladium, and nickel catalysts are commonly used in this reduction.



Examples

$$H—C\equiv C—CH_2CH_3 + 2H_2 \xrightarrow{Pt} H—CH_2—CH_2—CH_2CH_3$$

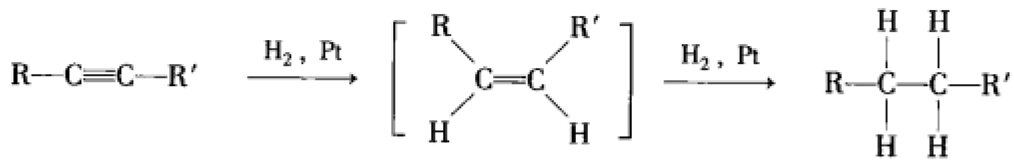
1-butyne → butane (100%)

$$CH_3—C\equiv C—CH_3 + 2H_2 \xrightarrow{Pt} CH_3—CH_2—CH_2—CH_3$$

2-butyne → butane (100%)

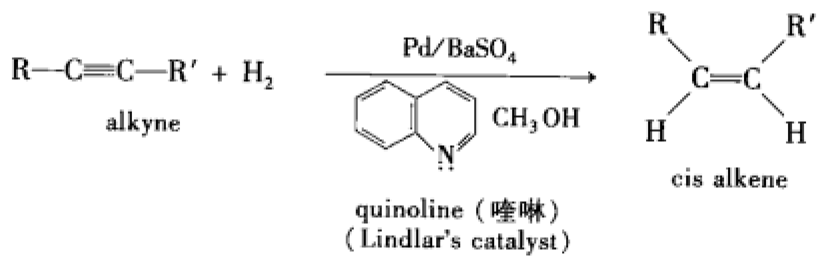
Catalytic hydrogenation takes place in two stages, with an alkene intermediate. With efficient catalysts such

as platinum, palladium, or nickel, it is usually impossible to stop the reaction at the alkene stage.



10-8B Catalytic Hydrogenation to cis Alkenes

Hydrogenation of an alkyne can be stopped at the alkene stage by using a "poisoned" (partially deactivated) catalyst made by treating a good catalyst with a compound that makes the catalyst less effective. **Lindlar's catalyst** is a poisoned palladium catalyst, composed of powdered barium sulfate coated with palladium, poisoned with quinoline. Nickel boride (Ni_2B) is a newer alternative to Lindlar's catalyst that is more easily made and often gives better yields.



The catalytic hydrogenation of alkynes is similar to the hydrogenation of alkenes, and both proceed with syn stereochemistry. In catalytic hydrogenation, the face of a pi bond contacts the solid catalyst, and the catalyst weakens the pi bond, allowing two hydrogen atoms to add (Figure 10-3). This simultaneous (or nearly simultaneous) addition of two hydrogen atoms on the same face of the alkyne ensures syn stereochemistry.

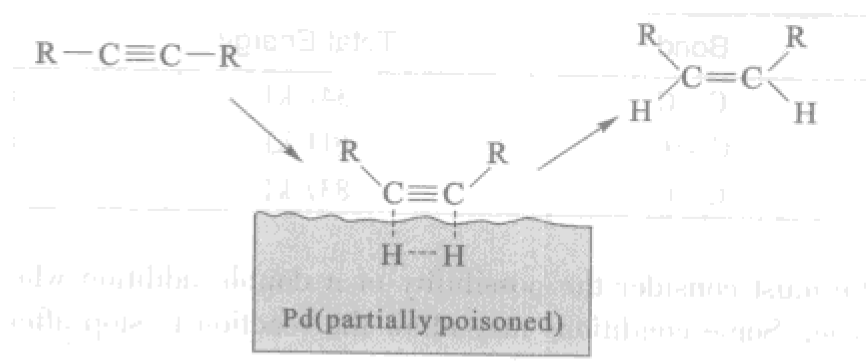
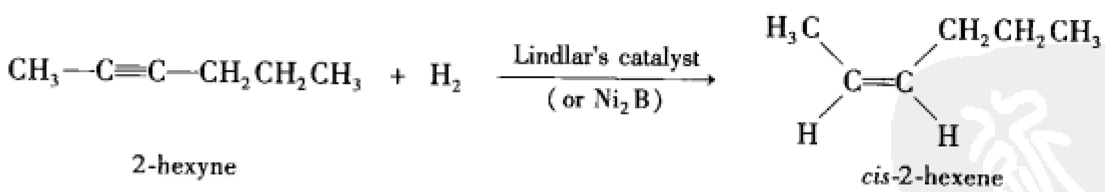


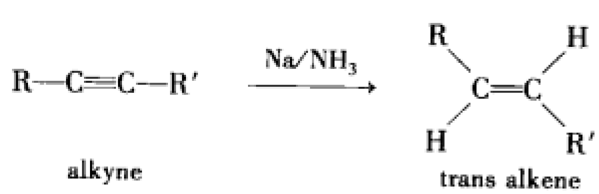
Figure 10-3 Catalytic hydrogenation of alkynes using the Lindlar catalyst.

In an internal alkyne, syn addition gives a cis product. For example, when 2-hexyne is hydrogenated using the Lindlar catalyst, the product is *cis*-2-hexene.

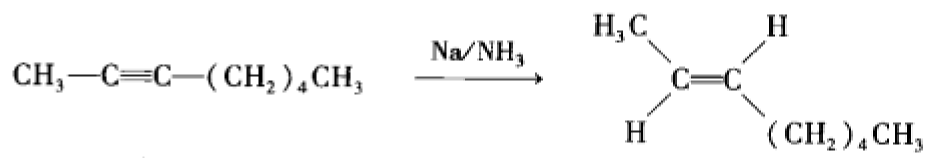


10-8C Metal-Ammonia Reduction to trans Alkenes

To form a trans alkene, two hydrogens must be added to the alkyne with anti stereochemistry. Sodium metal in liquid ammonia reduces alkynes with anti stereochemistry, so this reduction is used to convert alkynes to trans alkenes.



Example



2-octyne — *trans*-2-octene (80%)

Ammonia (bp −33 ℃) is a gas at room temperature, but it is kept liquid by using dry ice to cool the reaction vessel. As sodium dissolves in liquid ammonia, it gives up electrons, which produce a deep blue color. It is these solvated electrons that actually reduce the alkyne.

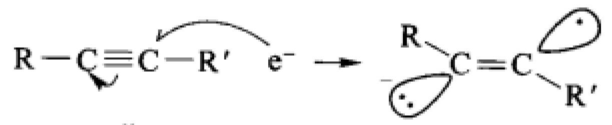
$$NH_3 + Na \longrightarrow \underset{\text{solvated electron}}{NH_3 \cdot e^-} \text{ (deep blue solution)} + Na^+$$

The metal-ammonia reduction proceeds by addition of an electron to the alkyne to form a radical anion, followed by protonation to give a neutral radical. Protons are provided by the ammonia solvent or by an alcohol added as a cosolvent. Addition of another electron, followed by another proton, gives the product.

MECHANISM 10-1 Metal-Ammonia Reduction of an Alkyne

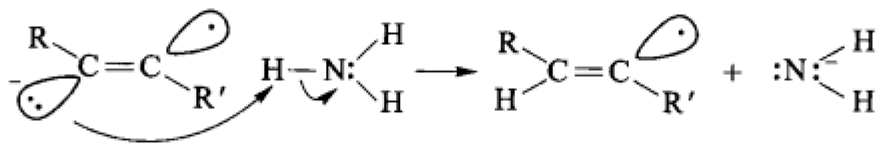
This mechanism involves addition of an electron, followed by a proton, then addition of a second electron, followed by a second proton.

Step 1: An electron adds to the alkyne, forming a radical anion.



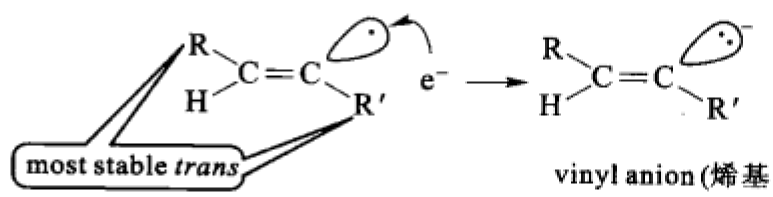
alkyne — radical anion (自由基负离子)

Step 2: The radical anion is protonated to give a radical.



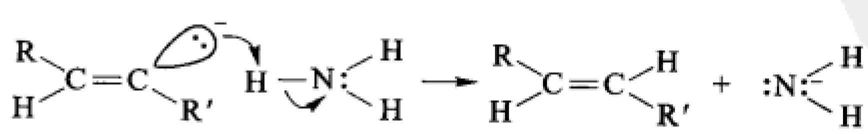
vinyl radical (烯基自由基)

Step 3: An electron adds to the radical, forming an anion.



vinyl anion (烯基负离子)

Step 4: Protonation of the anion gives an alkene.



trans alkene

The anti stereochemistry of the sodium-ammonia reduction appears to result from the greater stability of the vinyl radical in the trans configuration, where the alkyl groups are farther apart. An electron is added to the trans radical to give a trans vinyl anion, which is quickly protonated to the trans alkene.

PROBLEM 10-9

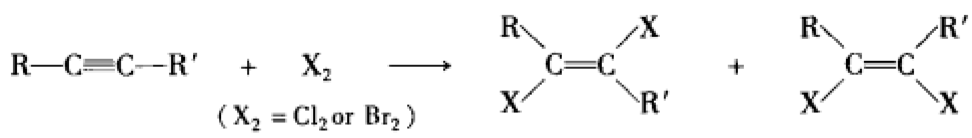
Show how you would convert

(a) 3-octyne to *cis*-3-octene (b) 2-pentyne to *trans*-2-pentene

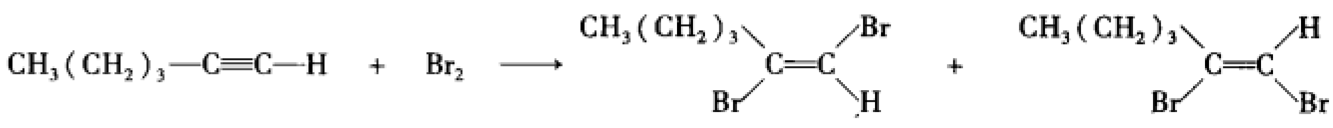
(c) *cis*-cyclodecene to *trans*-cyclodecene (d) *trans*-2-pentene to *cis*-2-pentene

10-8D Addition of Halogens

Bromine and chlorine add to alkynes just as they add to alkenes. If 1 mol of halogen adds to an alkyne, the product is a dihaloalkene. The stereochemistry of addition may be either syn or anti, and the products are often mixtures of cis and trans isomers.

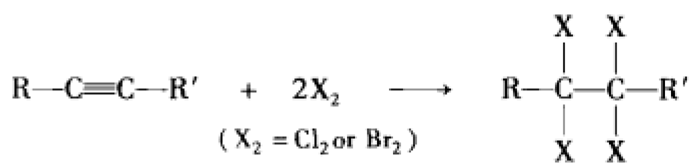


Example

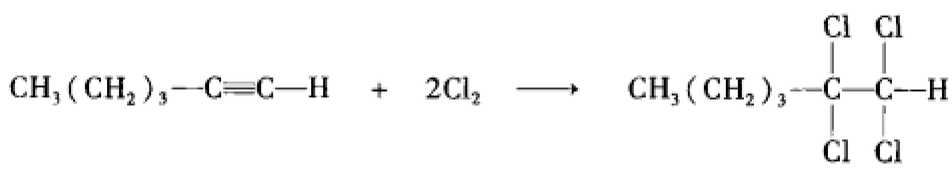


(72%) (28%)

If 2 mol of halogen add to an alkyne, a tetrahalide results. Sometimes it is difficult to keep the reaction from proceeding all the way to the tetrahalide even when we want it to stop at the dihalide.



Example



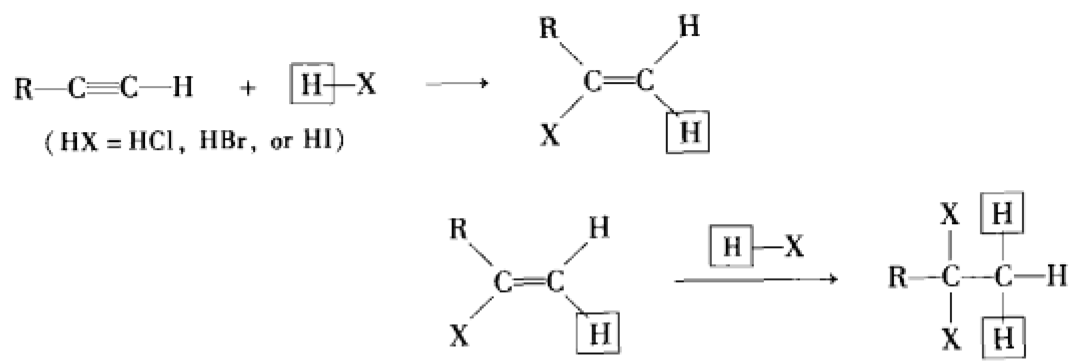
(100%)

PROBLEM 10-10

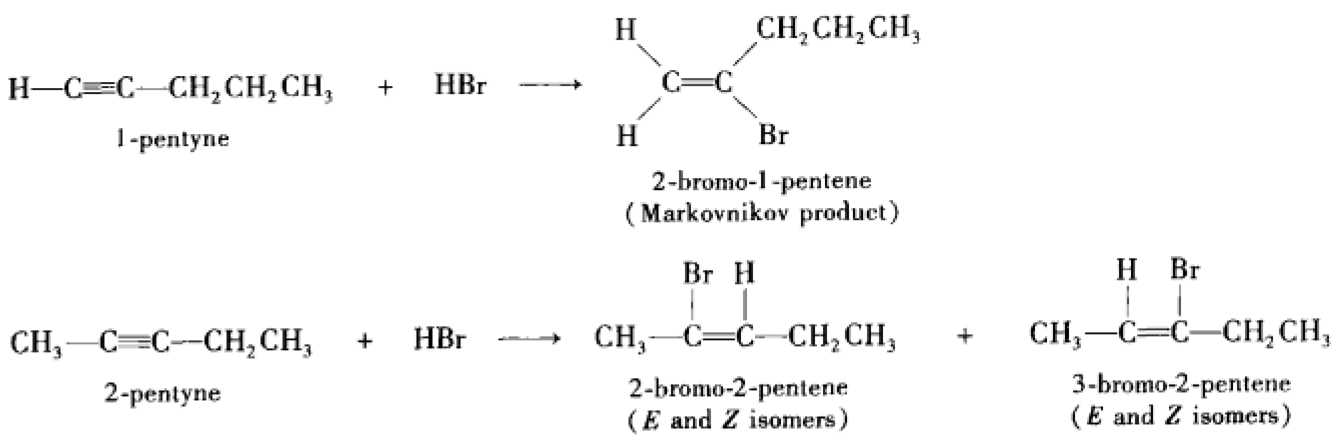
In the addition of just 1 mol of bromine to 1-hexyne, should the 1-hexyne be added to a bromine solution or should the bromine be added to the 1-hexyne? Explain your answer.

10-8E Addition of Hydrogen Halides

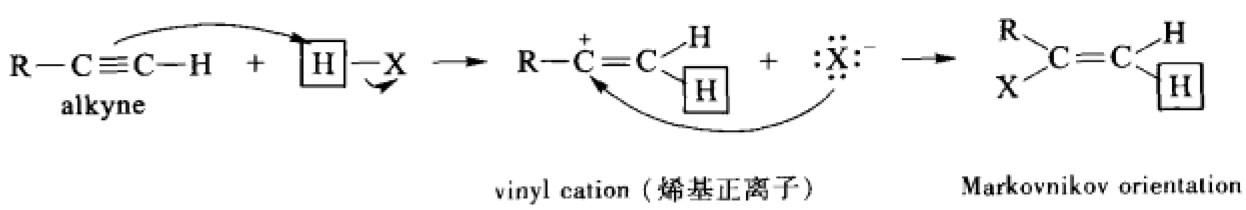
Hydrogen halides add across the triple bond of an alkyne in much the same way they add across the alkene double bond. The initial product is a vinyl halide. When a hydrogen halide adds to a terminal alkyne, the product has the orientation predicted by Markovnikov's rule. A second molecule of HX can add, usually with the same orientation as the first.



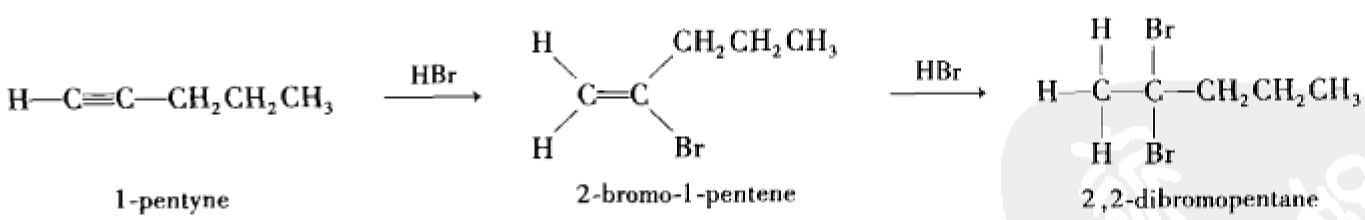
For example, the reaction of 1-pentyne with HBr gives the Markovnikov product. In an internal alkyne such as 2-pentyne, however, the acetylenic carbon atoms are equally substituted, and a mixture of products results.



The mechanism is similar to the mechanism of hydrogen halide addition to alkenes. The **vinyl cation** formed in the first step is more stable with the positive charge on the more highly substituted carbon atom. Attack by halide ion completes the reaction.



When 2 mol of a hydrogen halide add to an alkyne, the second mole usually adds with the same orientation as the first. This consistent orientation leads to a geminal dihalide. For example, a double Markovnikov addition of HBr to 1-pentyne gives 2,2-dibromopentane.



PROBLEM 10-11

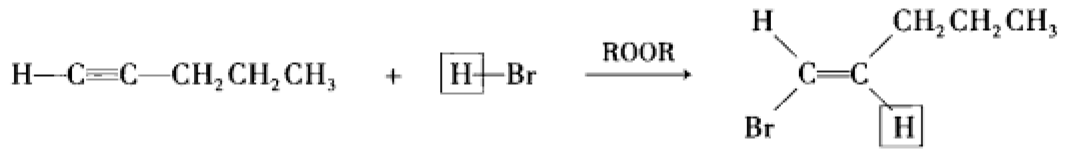
The reaction of 2-octyne with 2 equivalents of HCl gives a mixture of two products.

(**a**) Give the structures of the two products.

(**b**) Show why the second equivalent of HCl adds with the same orientation as the first in each case.

In Section 9-3B, we saw the effect of peroxides on the addition of HBr to alkenes. Peroxides catalyze a free-radical chain reaction that adds HBr across the double bond of an alkene in the anti-Markovnikov sense. A

similar reaction occurs with alkynes, with HBr adding with anti-Markovnikov orientation.



1-pentyne

1-bromo-1-pentene
(mixture of *E* and *Z* isomers)

PROBLEM 10-12

Propose a mechanism for the reaction of 1-pentyne with HBr in the presence of peroxides. Show why anti-Markovnikov orientation results.

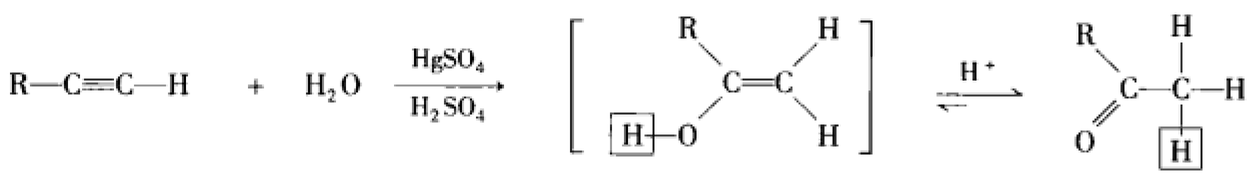
PROBLEM 10-13

Show how 1-hexyne might be converted to

(a) 1,2-dichloro-1-hexene
(b) 1-bromo-1-hexene
(c) 2-bromo-1-hexene
(d) 1,1,2,2-tetrabromohexane
(e) 2-bromohexane
(f) 2,2-dibromohexane

10-8F Hydration of Alkynes to Ketones and Aldehydes

Mercuric Ion-Catalyzed Hydration Alkynes undergo acid-catalyzed addition of water across the triple bond in the presence of mercuric ion as a catalyst. A mixture of mercuric sulfate in aqueous sulfuric acid is commonly used as the reagent. The hydration of alkynes is similar to the hydration of alkenes, and it also goes with Markovnikov orientation. The products are not the alcohols we might expect, however.

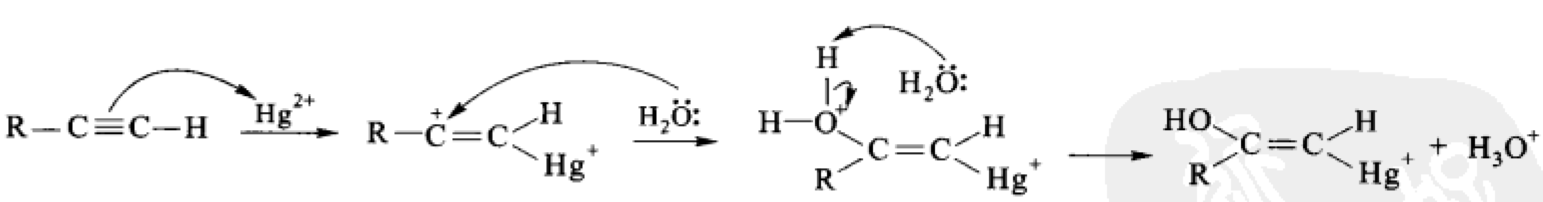


alkyne

a vinyl alcohol (enol) (烯醇)

ketone

Electrophilic addition of mercuric ion gives a vinyl cation, which reacts with water and loses a proton to give an organomercurial alcohol.

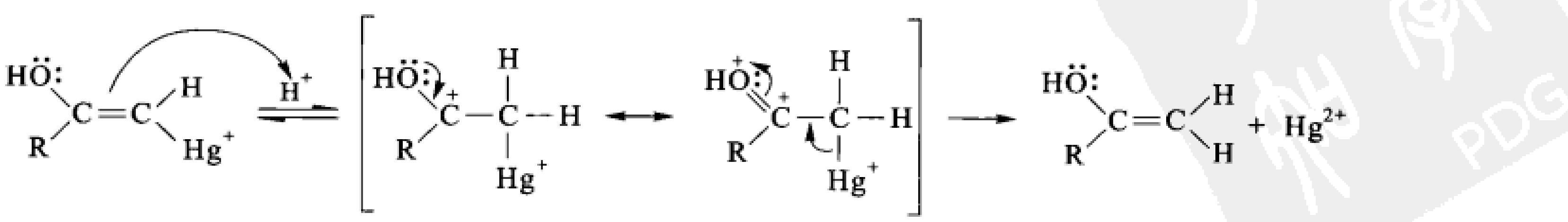


alkyne

vinyl cation

organomercurial alcohol (有机汞烯醇)

Under the acidic reaction conditions, mercury is replaced by hydrogen to give a vinyl alcohol, called an **enol**.

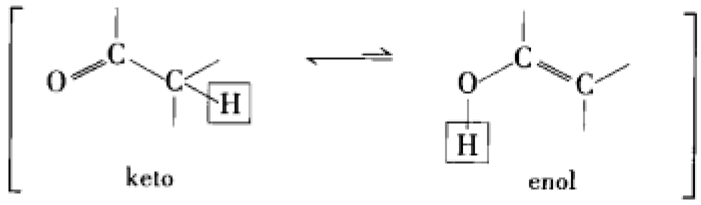


organomercurial alcohol

resonance-stabilized intermediate

vinyl alcohol
(enol)

Enols tend to be unstable and isomerize to the ketone form. As shown next, this isomerization involves the shift of a proton and a double bond. The (boxed) hydroxyl proton is lost, and a proton is regained at the methyl position, while the pi bond shifts from the C=C position to the C=O position. This type of rapid equilibrium is called a **tautomerism**. The one shown is the **keto-enol tautomerism**, which is covered in more detail in Chapter 23. The keto form usually predominates.



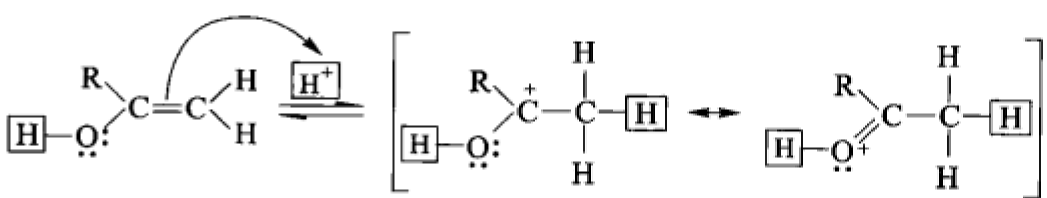
keto-enol tautomerism
(酮-烯醇互变异构)

In acidic solution, the keto-enol tautomerism takes place by addition of a proton to the adjacent carbon atom, followed by loss of the hydroxyl proton from oxygen.

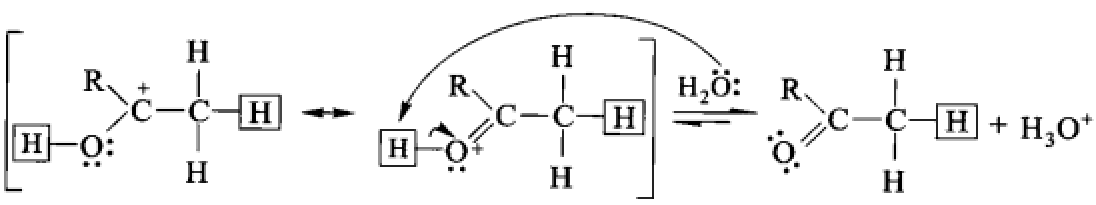
MECHANISM 10-2 Acid-Catalyzed Keto-Enol Tautomerism

Under acidic conditions, the proton first adds at its new position on the adjacent carbon atom, and then is removed from its old position in the hydroxyl group.

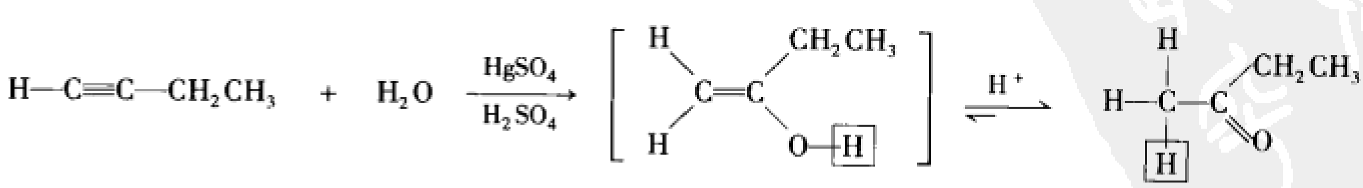
Step 1: Addition of a proton at the methylene group.



Step 2: Loss of the hydroxyl proton.



For example, the mercuric-catalyzed hydration of 1-butyne gives 1-buten-2-ol as an intermediate. In the acidic solution, the intermediate quickly equilibrates to its more stable keto tautomer, 2-butanone.

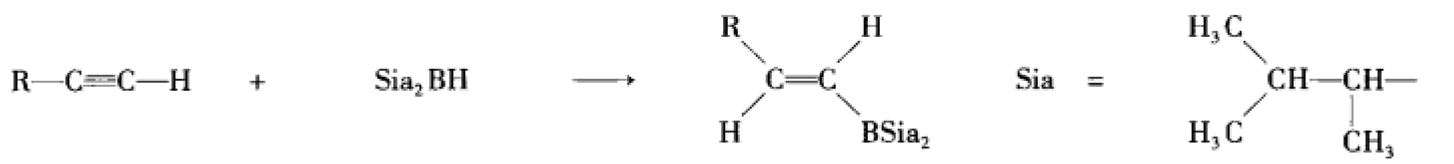


PROBLEM 10-14

When 2-pentyne reacts with mercuric sulfate in dilute sulfuric acid, the product is a mixture of two ketones. Give the structures of these products, and use mechanisms to show how they are formed.

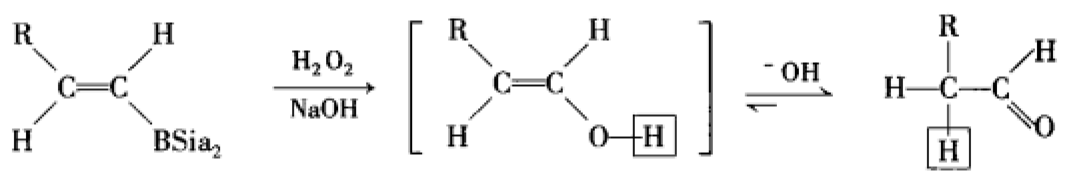
Hydroboration-Oxidation In Section 9-7 we saw that hydroboration-oxidation adds water across the double

bonds of alkenes with anti-Markovnikov orientation. A similar reaction takes place with alkynes, except that a hindered dialkylborane must be used to prevent addition of two molecules of borane across the triple bond. Di (secondary isoamyl) borane, called "disiamylborane," adds to the triple bond only once to give a vinylborane. (**Amyl** is an older common name for pentyl.) In a terminal alkyne, the boron atom bonds to the terminal carbon atom.



terminal alkyne — disiamylborane (二仲异戊基硼烷) — a vinylborane (烯基硼烷) — "*sec*-isoamyl" or "**siamyl**" (仲异戊基)

Oxidation of the vinylborane (using basic hydrogen peroxide) gives a vinyl alcohol (enol), resulting from anti-Markovnikov addition of water across the triple bond. This enol quickly tautomerizes to its more stable carbonyl (keto) form. In the case of a terminal alkyne, the keto product is an aldehyde. This sequence is an excellent method for converting terminal alkynes to aldehydes.



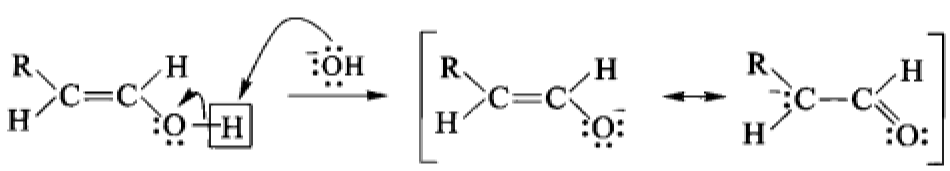
vinylborane — unstable enol form — aldehyde

Under basic conditions, the keto-enol tautomerism operates by a different mechanism than it does in acid. In base, the proton is first removed from its old position in the OH group, and then replaced on carbon. In acid, the proton was first added on carbon, and then removed from the hydroxyl group.

MECHANISM 10-3 Base-Catalyzed Keto-Enol Tautomerism

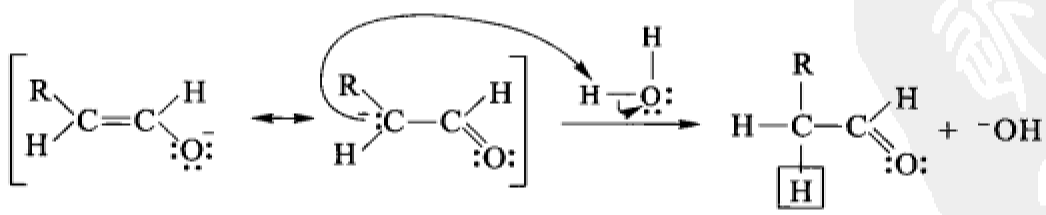
Under basic conditions, the proton is first removed from its old position in the enol, and then replaced in its new position on the adjacent carbon atom of the ketone or aldehyde.

***Step 1*:** Loss of the hydroxyl proton.



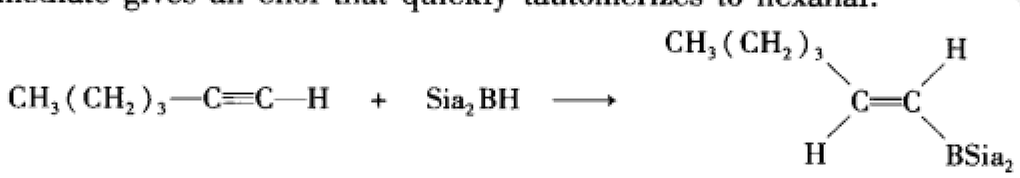
enol form — stabilized "enolate" ion

***Step 2*:** Reprotonation on the adjacent carbon atom.

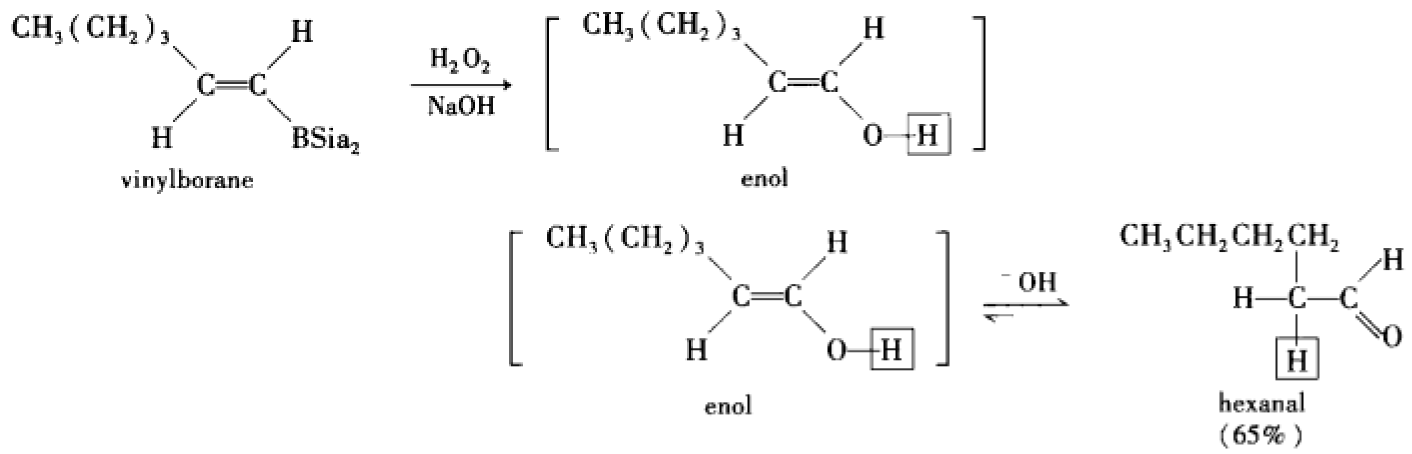


stabilized "enolate" ion — keto form

Hydroboration of 1-hexyne, for example, gives the vinylborane with boron on the less highly substituted carbon. Oxidation of this intermediate gives an enol that quickly tautomerizes to hexanal.



1-hexyne — a vinylborane



PROBLEM 10-15

For each compound, give the product(s) expected from (1) $HgSO_4/H_2SO_4$-catalyzed hydration and (2) hydroboration-oxidation.

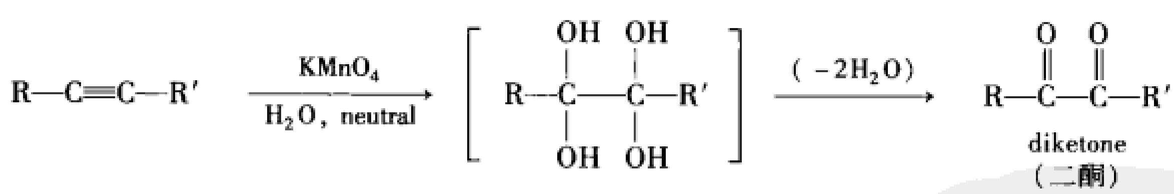
(a) 1-hexyne **(b)** 2-hexyne

(c) 3-hexyne **(d)** cyclodecyne

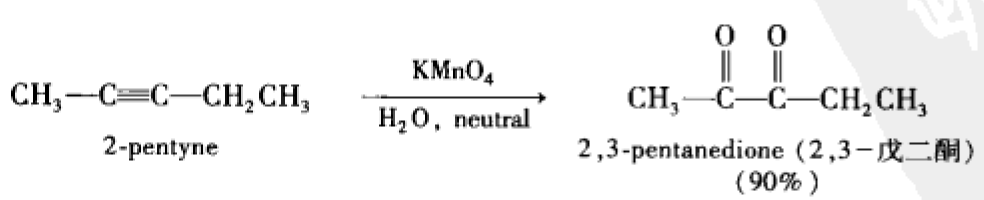
10-9 Oxidation of Alkynes

10-9A Permanganate Oxidations

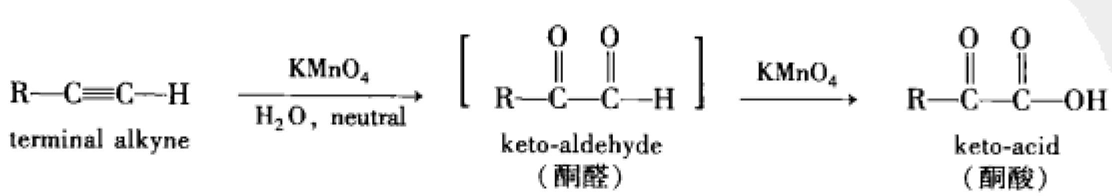
Under mild conditions, potassium permanganate oxidizes alkenes to glycols, compounds with two —OH groups on adjacent carbon atoms (Section 9-14B). Recall that this oxidation involves adding a hydroxyl group to each end of the double bond (hydroxylation). A similar reaction occurs with alkynes. If an alkyne is treated with aqueous potassium permanganate under nearly neutral conditions, an α-diketone results. This is conceptually the same as hydroxylating each of the two pi bonds of the alkyne, then losing two molecules of water to give the diketone.



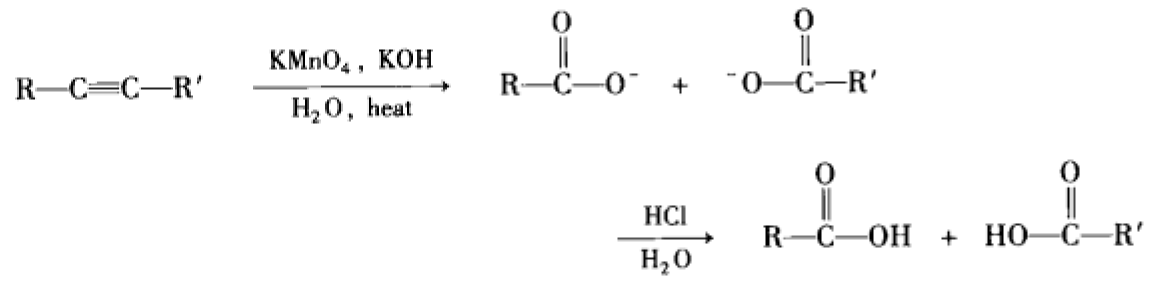
For example, when 2-pentyne is treated with a cold, dilute solution of neutral permanganate, the product is 2,3-pentanedione.



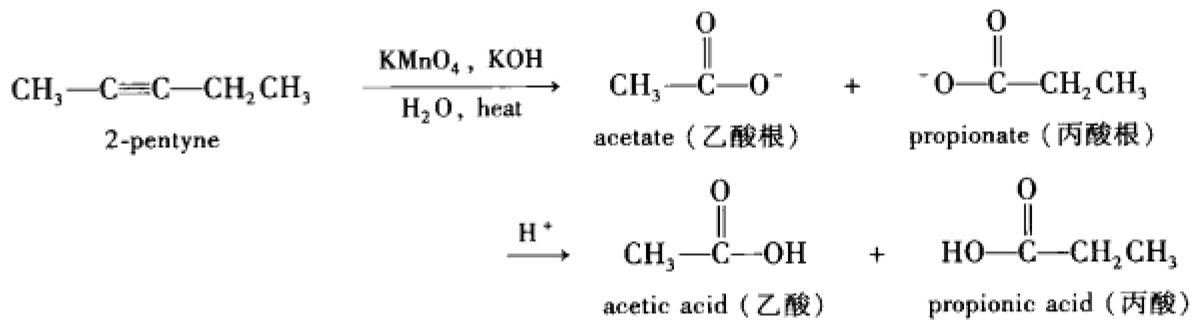
Terminal alkynes probably give a keto-aldehyde at first, but the aldehyde quickly oxidizes to an acid under these conditions.



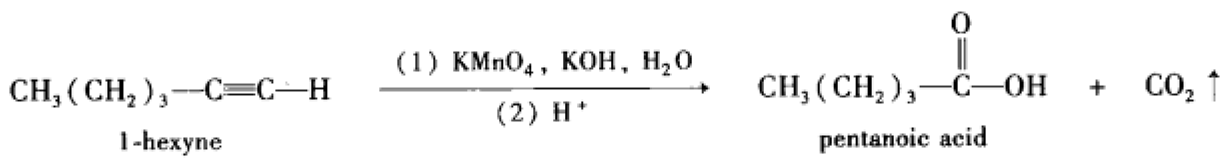
If the reaction mixture becomes warm or too basic, the diketone undergoes oxidative cleavage. The products are the salts of carboxylic acids, which can be converted to the free acids by adding dilute acid.



For example, warm, basic permanganate cleaves the triple bond of 2-pentyne to give acetate and propionate ions. Acidification reprotonates these anions to acetic acid and propionic acid.



Terminal alkynes are cleaved similarly to give a carboxylic acid and CO_2.

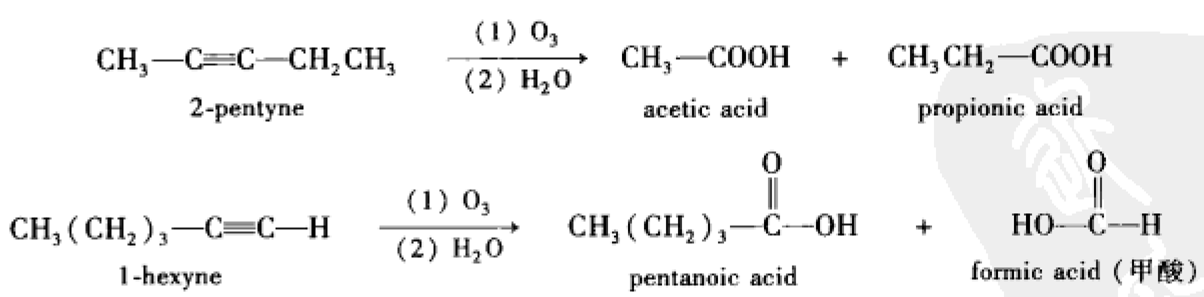


10–9B Ozonolysis

Ozonolysis of an alkyne, followed by hydrolysis, cleaves the triple bond and gives two carboxylic acids. Either permanganate cleavage or ozonolysis can be used to determine the position of the triple bond in an unknown alkyne (see Problem 10–17).

$$R{-}C{\equiv}C{-}R' \xrightarrow[(2)\ H_2O]{(1)\ O_3} R{-}COOH + R'{-}COOH$$

Examples



PROBLEM 10–16

Predict the product(s) you would expect from treatment of each compound with (1) dilute, neutral $KMnO_4$ and (2) warm, basic $KMnO_4$, then dilute acid.

(a) 1-hexyne (b) 2-hexyne (c) 3-hexyne
(d) 2-methyl-3-hexyne (e) cyclodecyne

PROBLEM 10-17

Oxidative cleavages can help to determine the positions of the triple bonds in alkynes.

(a) An unknown alkyne undergoes oxidative cleavage to give adipic acid and two equivalents of acetic acid. Propose a structure for the alkyne.

$$\text{unknown alkyne} \xrightarrow[\text{(2) } H_2O]{\text{(1) } O_3} \underset{\text{adipic acid (己二酸, 肥酸)}}{HOOC{-}(CH_2)_4{-}COOH} + 2CH_3COOH$$

(b) An unknown alkyne undergoes oxidative cleavage to give the following triacid plus one equivalent of propanoic acid. Propose a structure for the alkyne.

$$\text{unknown alkyne} \xrightarrow[\text{(2) } H_2O]{\text{(1) } O_3} \underset{\text{a triacid (三羧酸)}}{HOOC{-}(CH_2)_7{-}\overset{\overset{\displaystyle COOH}{|}}{C}H{-}COOH} + \underset{\text{propionic acid}}{CH_3CH_2COOH}$$

Summary in Chinese

本 章 概 要

一、炔烃的结构

炔烃中三键碳原子为 *sp* 杂化,两个碳原子之间形成一个 C(*sp*)—C(*sp*) σ 键,每个三键碳原子上有两个相互垂直的 2*p* 轨道,每个 2*p* 轨道上有一个电子,当两个碳原子相应的 *p* 轨道平行重叠时,形成两个 π 键。三键碳原子和与其相连接的原子或基团位于同一直线上。炔烃的两个三键碳原子之间的 π 电子云形成一个以 σ 键为对称轴的圆柱体形状。炔烃具有与烯烃相似的化学性质,能发生亲电加成、氧化和聚合等反应。

二、炔烃的物理性质

由于炔烃为线性分子,在液态和固态中,分子彼此易接近,分子间范德华力作用较强,简单炔烃的沸点、熔点及相对密度一般稍高于碳原子数相同的烷烃和烯烃。同系列炔烃,沸点随相对分子质量增加而升高。正构炔烃的沸点高于同碳数带支链的炔烃。与烷烃、烯烃相似,炔烃不溶于水,易溶于有机溶剂。

三、端炔的酸性

在端位炔烃中,与 *sp* 杂化的碳原子直接成键的氢原子称为炔氢,具有弱酸性,炔氢的酸性比氨强,但比水弱。因此,炔氢能与 $^-NH_2$、R^- 等强碱反应,生成金属炔化物,不能与 ^-OH、^-OR 等普通的碱反应。炔氢与强碱的反应(reactions of acetylenic hydrogen, Section 10-5)如下:

$$R{-}C{\equiv}C{-}H + NaNH_2 \longrightarrow R{-}C{\equiv}C{:}^-\,{}^+Na + NH_3$$

$$R{-}C{\equiv}C{-}H + R'Li \longrightarrow R{-}C{\equiv}CLi + R'H$$

$$R{-}C{\equiv}C{-}H + R'MgX \longrightarrow R{-}C{\equiv}CMgX + R'H$$

炔离子是强碱,同时也是良好的亲核试剂,可用于合成各种取代炔烃。

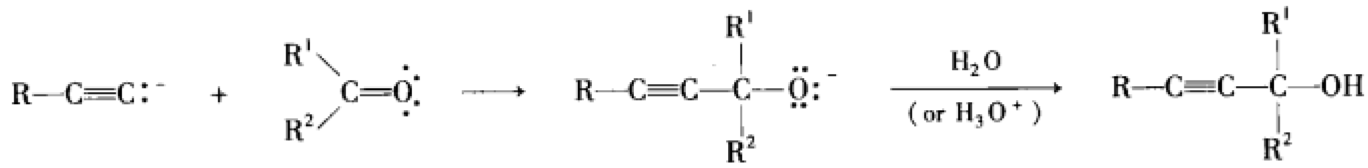
四、炔烃的制备 (preparation of alkynes)

1. 炔离子烷基化反应(alkylation of acetylide ions, Section 10-6A):

$$R{-}C{\equiv}C{:}^- + R'{-}X \xrightarrow{S_N2} R{-}C{\equiv}C{-}R' + X^-$$

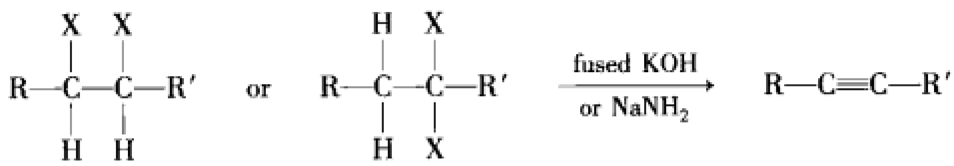
☆ 此反应为卤代烷的 S_N2 亲核取代反应，必须采用无空阻的伯卤代烷为反应物。炔离子($RC\equiv C^-$)为强碱，如用仲或叔卤代烷作为反应物，则发生 E2 消除反应，生成烯烃。

2. 炔离子对羰基的加成反应(additions of acetylide ions to carbonyl groups, Section 10-6B)：

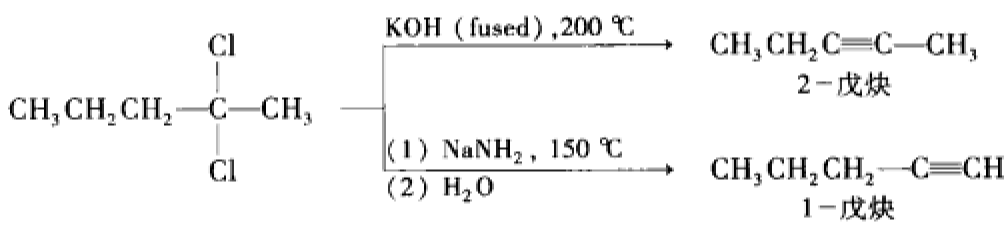


☆ 炔离子对羰基的亲核加成反应可用于合成各种炔丙醇骨架的炔醇衍生物。炔离子与甲醛、醛和酮反应可分别得到伯、仲、叔醇。

3. 二卤代烷双重脱卤化氢反应(double dehydrohalogenation of alkyl dihalides, Section 10-7)：



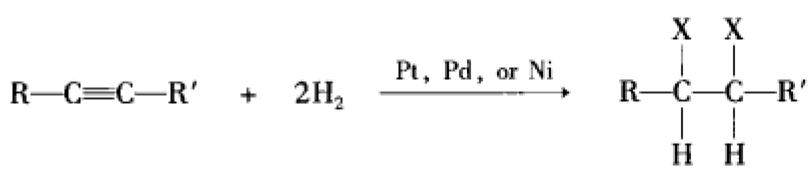
☆ 第二步烯基卤代烷的脱卤化氢反应必须在高温强碱存在下才能进行，反应物分子中不能有对强碱敏感的基团。在强碱存在下，炔烃分子中的三键经过丙二烯中间体发生位置异构化，KOH 为碱时生成内炔烃，而 $NaNH_2$ 为碱时生成端炔烃。比较 2,2-二氯戊烷在不同条件下的脱卤化氢反应：



五、炔烃的化学性质

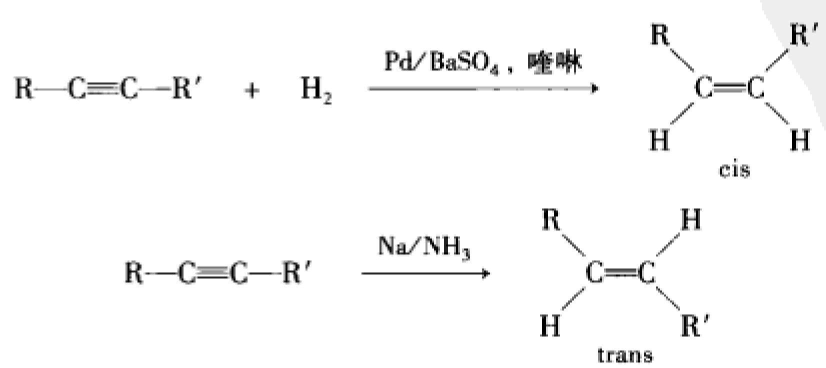
1. 炔烃三键的加成反应(additions to the triple bond of alkynes)：

(1) 炔烃还原至烷烃的反应(reduction of alkynes to alkanes, Section 10-8A)：



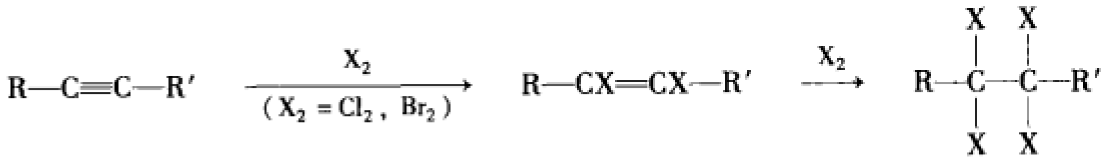
☆ 用 Pt、Pd、Ni 作催化剂时，加氢反应不能停止在烯烃阶段，只能得到三键彻底加氢产物——烷烃。反应物中不能有其他对加氢反应活泼的基团。

(2) 炔烃还原至烯烃的反应(reduction of alkynes to alkenes, Section 10-8B, 10-8C)：



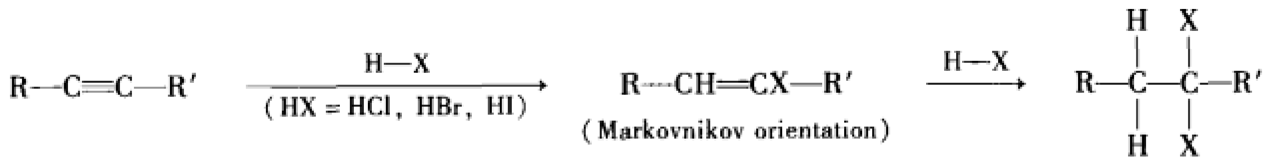
☆ 使用 Lindlar 催化剂($Pd/BaSO_4$，喹啉)或 Ni_2B 催化剂时，炔烃顺式加一分子氢生成烯烃。使用金属钠或锂作还原剂在液氨中反应时，炔烃反式加一分子氢。由这两种加氢反应，可从内炔烃出发，立体选择性地合成顺式或反式烯烃。

(3) 炔烃加卤素反应(addition of halogens, Section 10-8D)

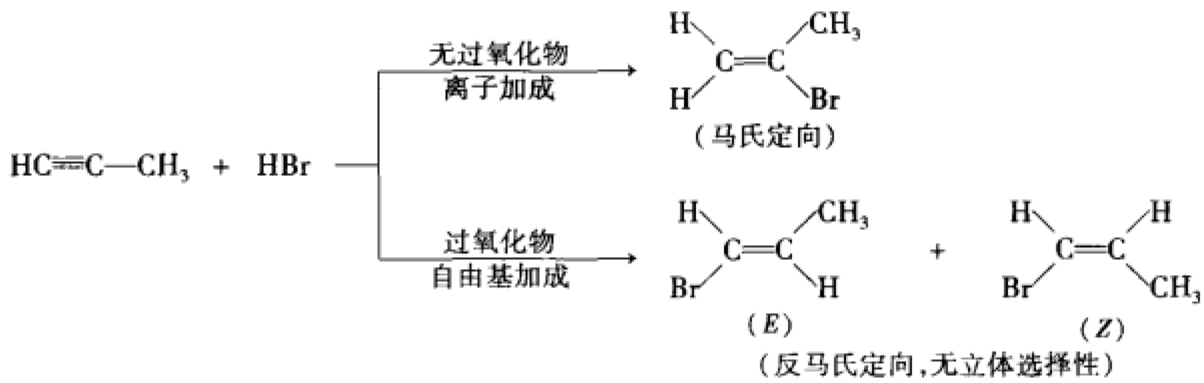


☆ 通过控制加入卤素的量，可以使反应停止在烯烃阶段，炔烃加卤素反应无立体选择性，同时生成顺式和反式二卤代烯烃。在过量卤素存在下，可高产率地合成四卤代烷烃。

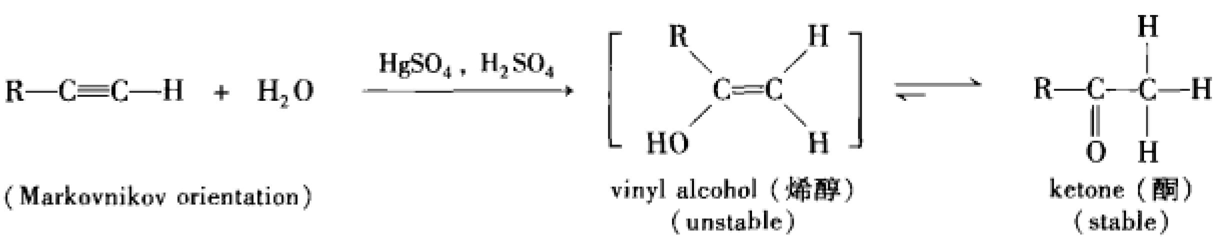
(4) 炔烃加卤化氢反应(addition of hydrogen halides, Section 10-8E)：



☆ 反应经过碳正离子机理，两步加成反应均符合马氏规则。与烯烃相同，炔烃加溴化氢反应亦存在过氧化物效应，即在过氧化物存在下，加成反应为反马氏定向。比较丙炔在不同条件下加溴化氢的反应：

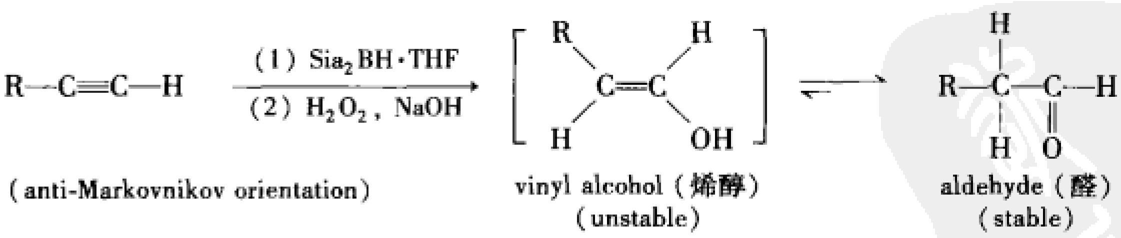


(5) 汞离子催化炔烃加水反应(mercuric ion-catalyzed hydration, Section 10-8F)：



☆ 一般炔烃亲电加成反应活性不如烯烃，有些亲电加成反应要有催化剂才能顺利进行。炔烃加水反应通常用汞盐作催化剂，生成中间产物烯醇(enol)，经过互变异构(tautomerization)最终生成醛或酮。以乙炔为反应物时得到乙醛，其他端炔烃水合反应均生成甲基酮，是实验室合成各种甲基酮的有效方法。内炔烃的加水反应没有区域选择性(regioselectivity)，同时生成两种酮，合成应用价值不大。

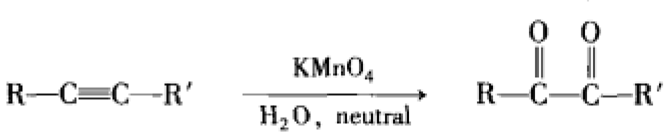
(6) 炔烃的硼氢化-氧化反应(hydroboration-oxidation, Section 10-8F)：



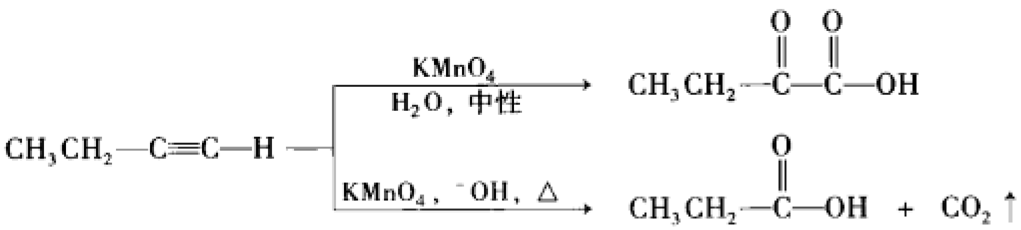
☆ 反应为顺式加成，反马氏定向。为使硼氢化反应停止在烯烃阶段，必须使用空阻大的二烷基硼氢化物。烯基硼烷中间产物在碱性过氧化氢中，首先生成烯醇，经过互变异构生成醛或酮。当反应物为端炔时得到醛，为内炔烃时得到酮。炔烃的硼氢化反应是实验室合成醛、酮的便利方法。

2. 炔烃的氧化反应(oxidation of alkynes, Section 10-9)：

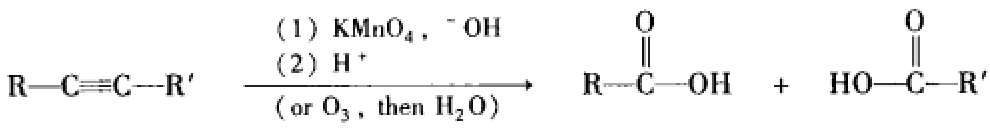
(1) 炔烃氧化为 α-二酮(oxidation to α-diketone, Section 10-9A)



☆ 在温和条件下，中性水溶液中，高锰酸钾将内炔烃氧化为 α－二酮，将端炔烃氧化为 α－酮酸（α-keto-acid）。在碱性水溶液中加热反应时，高锰酸钾使炔烃三键氧化断裂（oxidative cleavage），内炔烃生成相应的羧酸，端炔烃生成羧酸和二氧化碳。比较在不同条件下高锰酸钾氧化 1－丁炔的反应：



（2）炔烃三键氧化断裂（oxidative cleavage of the triple bond，Section 10－9B）



☆ 炔烃臭氧氧化与在碱性介质中加热高锰酸钾氧化炔烃产物相同。

Essential Problem-Solving Skills in Chapter 10

1. Explain why alkynes are more acidic than alkanes and alkenes. Show how to generate nucleophilic acetylide ions and heavy-metal acetylides.
2. Propose effective single-step and multistep syntheses of alkynes.
3. Predict the products of additions, oxidations, reductions, and cleavages of alkynes, including orientation of reaction (regiochemistry) and stereochemistry.
4. Use alkynes as starting materials and intermediates in one-step and multistep syntheses.
5. Show how the reduction of an alkyne leads to an alkene or alkene derivative with the desired stereochemistry.

Study Problems

10－18 Briefly define each term, and give an example.

(a) alkyne（炔） (b) acetylide ion（乙炔基负离子）
(c) enol（烯醇） (d) tautomerism（互变异构）
(e) Lindlar's catalyst（催化剂） (f) disiamylborane（二仲异戊基硼烷）
(g) vinyl cation（乙烯基正离子） (h) oxidative cleavage of an alkyne（炔氧化断裂）
(i) hydration of an alkyne（炔加水反应） (j) hydroboration of an alkyne（炔硼氢化反应）

10－19 Predict the products of reaction of 1-pentyne with the following reagents.

(a) 1 equivalent of HCl (b) 2 equivalents of HCl (c) excess H_2, Ni
(d) H_2, $Pd/BaSO_4$, quinoline (e) 1 equivalent of Br_2 (f) 2 equivalents of Br_2
(g) cold, dilute $KMnO_4$ (h) warm, concd. $KMnO_4$, NaOH (i) Na, liquid ammonia
(j) $NaNH_2$ (k) $H_2SO_4/HgSO_4$, H_2O (l) Sia_2BH, then H_2O_2, ^-OH

10－20 Show how you would accomplish the following synthetic transformations. Show all intermediates.

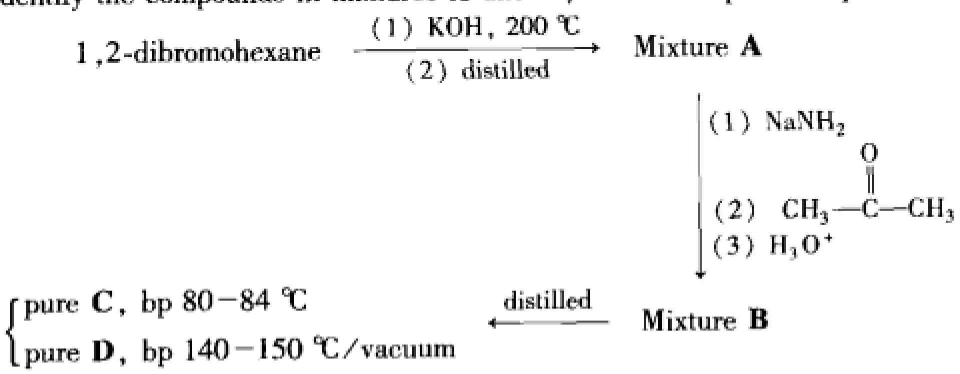
(a) 2,2-dibromobutane ⟶ 1-butyne
(b) 2,2-dibromobutane ⟶ 2-butyne
(c) 1-butyne ⟶ 3-octyne
(d) *trans*-2-hexene ⟶ 2-hexyne
(e) *cis*-2-hexene ⟶ 1-hexyne
(f) cyclodecyne ⟶ *cis*-cyclodecene
(g) cyclodecyne ⟶ *trans*-cyclodecene

(h) 1-hexyne ⟶ 2-hexanone, $CH_3COCH_2CH_2CH_2CH_3$

(i) 1-hexyne ⟶ hexanal, $CH_3(CH_2)_4CHO$

(j) *trans*-2-hexene ⟶ *cis*-2-hexene

10–21 Potassium hydroxide is mixed with 1,2-dibromo-4,4-dimethylpentane, and the mixture is heated at 200 ℃ in a sealed tube for 1 hour. The product mixture is distilled, and the distillate is collected over a boiling range of 75–85 ℃ to give mixture (**A**) of two compounds. This mixture is treated with sodium amide, followed by acetone, then by dilute acid, to give another product mixture (**B**). Mixture **B** is distilled, with one component (**C**) collected between 80–84 ℃ and another component (**D**) collected between 140–150 ℃ under a good vacuum. Further analysis shows that product **D** contains a hydroxyl group. Identify the compounds in mixtures **A** and **B**, as well as pure compounds **C** and **D**.



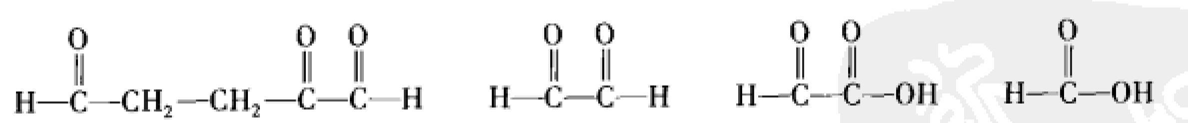
10–22 Predict the products formed when $CH_3CH_2—C{\equiv}C\!:^-\,Na^+$ reacts with the following compounds.

(a) ethyl bromide
(b) *t*-butyl bromide
(c) formaldehyde
(d) cyclohexanone
(e) $CH_3CH_2CH_2CHO$
(f) cyclohexanol
(g) 2-butanone, $CH_3CH_2COCH_3$

10–23 Show how you would synthesize the following compounds, starting with acetylene and any compounds containing no more than four carbon atoms.

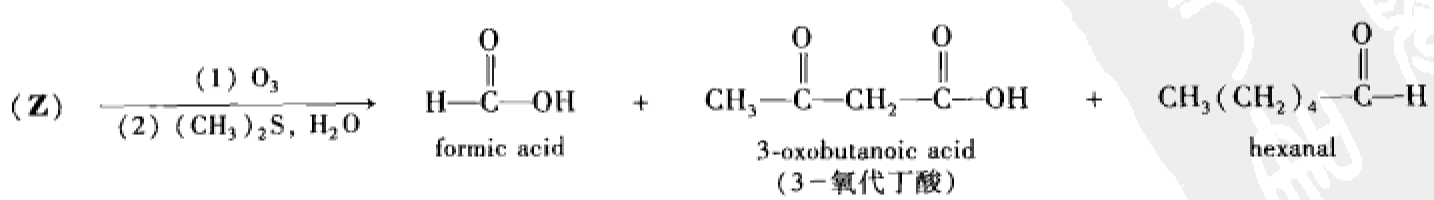
(a) 1-hexyne
(b) 2-hexyne
(c) *cis*-2-hexene
(d) *trans*-2-hexene
(e) hexane
(f) 2,2-dibromohexane
(g) pentanal, $CH_3CH_2CH_2CH_2CHO$
(h) 2-pentanone, $CH_3—CO—CH_2CH_2CH_3$
(i) (±)-3,4-dibromohexane
(j) *meso*-2,3-butanediol

10–24 When treated with hydrogen and a platinum catalyst, an unknown compound (**X**) absorbs 5 equivalents of hydrogen to give *n*-butylcyclohexane. Treatment of **X** with an excess of ozone, followed by dimethyl sulfide and water, gives the following products:



Propose a structure for the unknown compound (**X**). Is there any uncertainty in your structure?

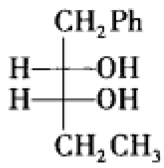
10–25 When compound (**Z**) is treated with ozone, followed by dimethyl sulfide and washing with water, the products are formic acid, 3-oxobutanic acid, and hexanal.



Propose a structure for compound (**Z**). What uncertainty is there in the structure you have proposed?

10–26 Show how you would synthesize the following compounds from acetylene and any other needed reagents:

(a) 6-phenylhex-1-en-4-yne
(b) *cis*-1-phenyl-2-pentene
(c) *trans*-1-phenyl-2-pentene

(d) 

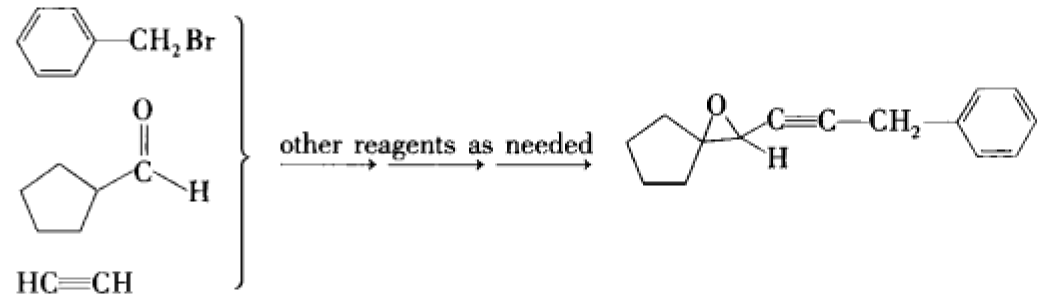
(and its enantiomer)

***10−27** Using any necessary inorganic reagents, show how you would convert acetylene and isobutyl bromide to

(a) *meso*-2,7-dimethyl-4,5-octanediol, $(CH_3)_2CHCH_2CH(OH)CH(OH)CH_2CH(CH_3)_2$

(b) (±)-2,7-dimethyl-4,5-octanediol

***10−28** Show how you would convert the following starting materials into the target compound. You may use any additional reagents you need.

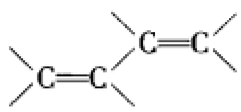


Chapter 11

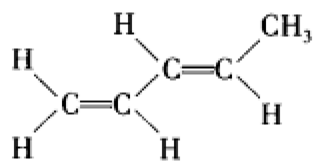
Conjugated Systems and Orbital Symmetry

11-1 Introduction

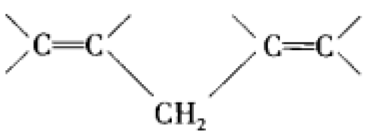
Double bonds can interact with each other if they are separated by just one single bond. Such interacting double bonds are said to be **conjugated.** Double bonds with two or more single bonds separating them have little interaction and are called **isolated double bonds.** For example, 1,3-pentadiene has conjugated double bonds, and 1,4-pentadiene has isolated double bonds.



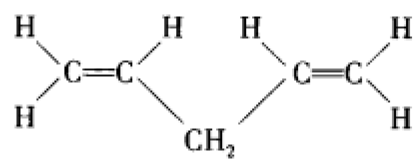
conjugated double bonds（共轭双键）
(more stable than isolated double bonds)



1,3-pentadiene



isolated double bonds（隔离双键）

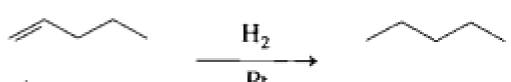


1,4-pentadiene

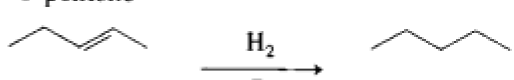
Because of the interaction between the double bonds, systems containing conjugated double bonds tend to be more stable than similar systems with isolated double bonds. In this chapter, we consider the unique properties of conjugated systems, the theoretical reasons for this extra stability, and some of the characteristic reactions of molecules containing conjugated double bonds. We also study ultraviolet spectroscopy, a tool for determining the structures of conjugated systems.

11-2 Stabilities of Dienes

In Chapter 8, we used **heats of hydrogenation** to compare the relative stabilities of alkenes. For example, the heats of hydrogenation of 1-pentene and *trans*-2-pentene show that the disubstituted double bond in *trans*-2-pentene is 10 kJ/mol more stable than the monosubstituted double bond in 1-pentene.

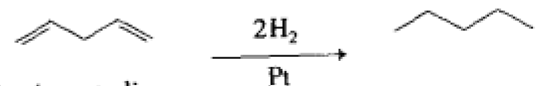


1-pentene $\Delta H^\ominus = -126$ kJ/mol



trans-2-pentene $\Delta H^\ominus = -116$ kJ/mol

When a molecule has two isolated double bonds, the heat of hydrogenation is close to the sum of the heats of hydrogenation for the individual double bonds. For example, the heat of hydrogenation of 1,4-pentadiene is −252 kJ/mol, about twice that of 1-pentene.



1,4-pentadiene $\Delta H^\ominus = -252$ kJ/mol

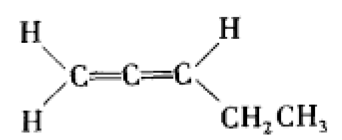
For conjugated dienes, the heat of hydrogenation is less than the sum for the individual double bonds. For example, *trans*-1,3-pentadiene has a monosubstituted double bond like the one in 1-pentene and a disubstituted double bond like the one is 2-pentene. The sum of the heats of hydrogenation of 1-pentene and 2-pentene is −242 kJ, but the heat of hydrogenation of *trans*-1,3-pentadiene is −225 kJ/mol, showing that the conjugated diene has about 17 kJ/mol extra stability.

1-pentene + 2-pentene = predicted
(−126 kJ) + (−116 kJ) = −242 kJ/mol

trans-1,3-pentadiene

actual value −225 kJ/mol
more stable by 17 kJ/mol

What happens if two double bonds are even closer together than in the conjugated case? Successive double bonds with no intervening single bonds are called **cumulated double bonds.** Consider 1,2-pentadiene, which contains cumulated double bonds. Such 1,2-diene systems are also called **allenes**, after the simplest member of the class, 1,2-propadiene or "allene," $H_2C=C=CH_2$. The heat of hydrogenation of 1,2-pentadiene is −292 kJ/mol.



1,2-pentadiene (ethylallene) $\xrightarrow[\text{Pt}]{H_2}$ $CH_3CH_2CH_2CH_2CH_3$ (pentane) $\Delta H^\ominus = -292$ kJ/mol

sum of 1-pentene + 2-pentene $\Delta H^\ominus = -242$ kJ/mol
1,2-pentadiene is *less* stable by 50 kJ/mol

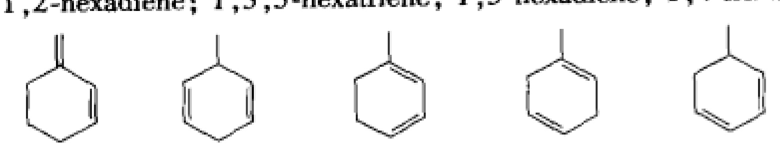
Because 1,2-pentadiene has a larger heat of hydrogenation than 1,4-pentadiene, we conclude that the cumulated double bonds of allenes are less stable than isolated double bonds and much less stable than conjugated double bonds. Figure 11−1 summarizes the relative stability of isolated, conjugated, and cumulated dienes and compares them with alkynes.

PROBLEM 11−1

Rank each group of compounds in order of increasing heat of hydrogenation.

(a) 1,2-hexadiene; 1,3,5-hexatriene; 1,3-hexadiene; 1,4-hexadiene; 1,5-hexadiene; 2,4-hexadiene

(b)



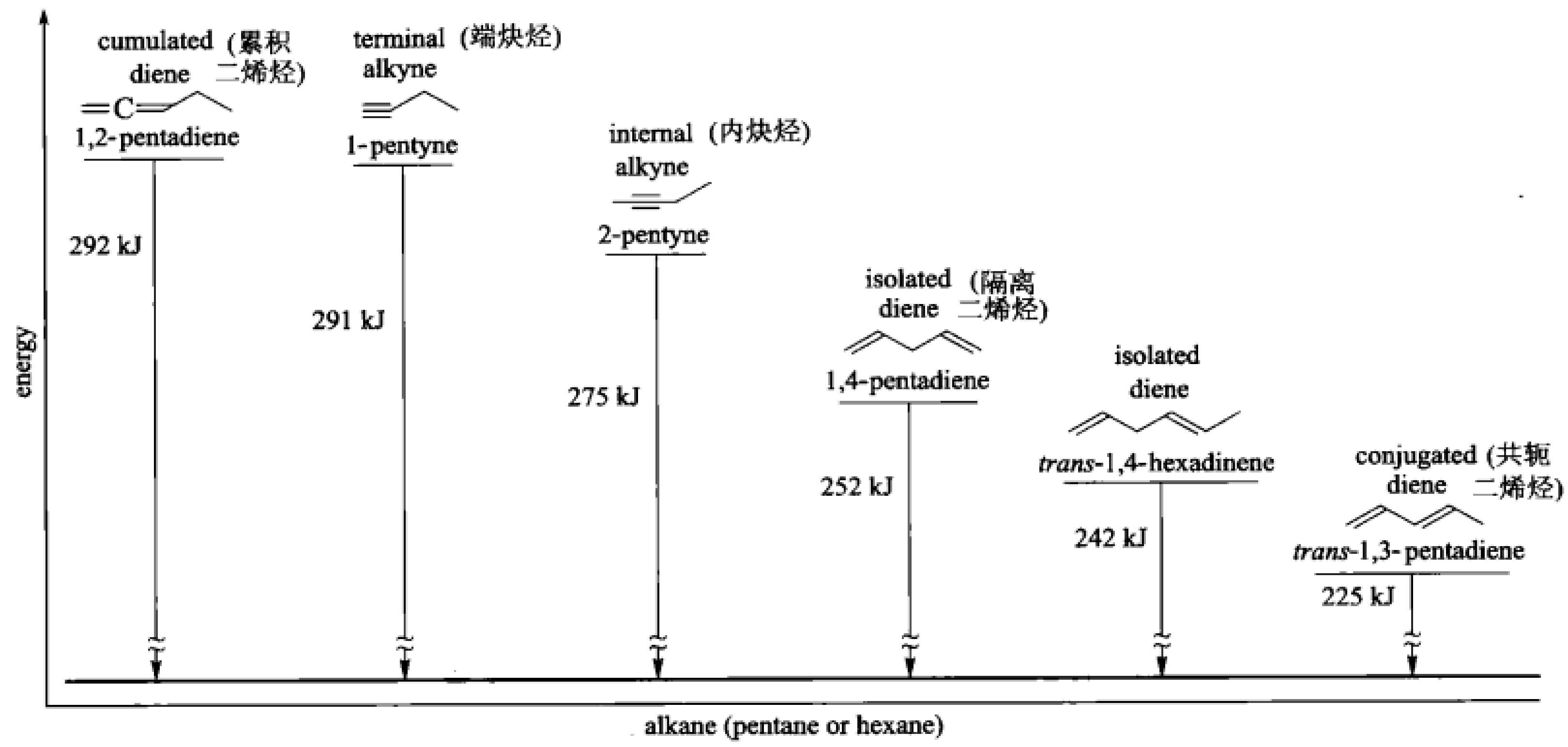


Figure 11-1 Relative energies of conjugated, isolated, and cumulated dienes compared with alkynes, based on heats of hydrogenation (kJ/mol).

PROBLEM 11-2

In a strongly acidic solution, 1,4-cyclohexadiene tautomerizes to 1,3-cyclohexadiene. Propose a mechanism for this rearrangement, and explain why it is energetically favorable.

PROBLEM 11-3

(Review) The central carbon atom of an allene is a member of two double bonds, and it has an interesting orbital arrangement that holds the two ends of the molecule at right angles to each other.

(a) Draw an orbital diagram of allene, showing why the two ends are perpendicular.

(b) Draw the two enantiomers of 1,3-dichloroallene. A model may be helpful.

11-3 Molecular Orbitals of a Conjugated System

Figure 11-1 shows that the compound with conjugated double bonds is 17 kJ/mol more stable than a similar compound with isolated double bonds. This 17 kJ/mol of extra stability in the conjugated molecule is called the **resonance energy** of the system. (Other terms favored by some chemists are *conjugation energy*, *delocalization energy*, and *stabilization energy*.) We can best explain this extra stability of conjugated systems by examining their **molecular orbitals.** Let's begin with the molecular orbitals of the simplest conjugated diene, 1,3-butadiene.

11-3A Structure and Bonding of 1,3-Butadiene

The heat of hydrogenation of 1,3-butadiene is about 17 kJ/mol less than twice that of 1-butene, showing that 1,3-butadiene has a resonance energy of 17 kJ/mol.

$$H_2C{=}CH{-}CH{=}CH_2 \xrightarrow{H_2,\ Pt} CH_3{-}CH_2{-}CH_2{-}CH_3 \qquad \Delta H^{\ominus} = -237\ \text{kJ/mol}$$

1,3-butadiene

$$H_2C{=}CH{-}CH_2{-}CH_3 \xrightarrow{H_2,\ Pt} CH_3{-}CH_2{-}CH_2{-}CH_3 \qquad \Delta H^{\ominus} = -127\ \text{kJ/mol}$$

1-butene $\times\ 2 = -254$ kJ/mol

resonance energy of 1,3-butadiene = 254 kJ/mol − 237 kJ/mol = 17 kJ/mol

Figure 11−2 shows the most stable conformation of 1,3-butadiene. Note that this conformation is planar, with the *p* orbitals on the two pi bonds aligned.

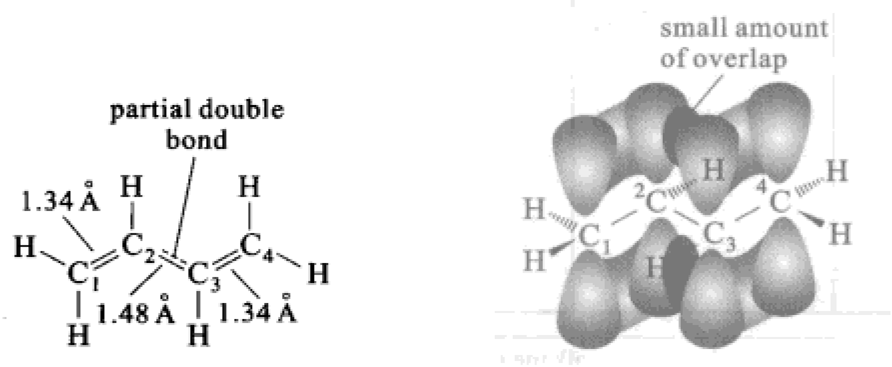


Figure 11−2 Structure of 1,3-butadiene in its most stable conformation. The 1.48 Å central carbon-carbon single bond is shorter than the 1.54 Å bonds typical of alkanes because of its partial double-bond character.

The C2—C3 bond in 1,3-butadiene (1.48 Å) is considerably shorter than a carbon-carbon single bond in an alkane (1.54 Å). This bond is shortened slightly by the increased *s* character of the sp^2 hybrid orbitals, but the most important cause of this bond shortening is its pi bonding overlap and partial double-bond character. The planar conformation, with the *p* orbitals of the two double bonds aligned, allows overlap between the pi bonds. In effect, the electrons in the double bonds are **delocalized** over the entire molecule, creating some pi overlap and pi bonding in the C2—C3 bond. The length of this bond is intermediate between the normal length of a single bond and that of a double bond.

Lewis structures are not adequate to represent delocalized molecules such as 1,3-butadiene. To represent the bonding in conjugated systems accurately, we must consider molecular orbitals that represent the entire conjugated pi system, and not just one bond at a time.

11−3B Constructing the Molecular Orbitals of 1,3-Butadiene

All four carbon atoms of 1,3-butadiene are sp^2 hybridized, and (in the planar conformation) they all have overlapping *p* orbitals. Let's review how we constructed the pi molecular orbitals (MOs) of ethylene from the *p* atomic orbitals of the two carbon atoms (Figure 11−3). Each *p* orbital consists of two lobes, with opposite phases of the wave function in the two lobes. The plus and minus signs used in drawing these orbitals indicate the *phase of the wave function*, **not electrical charges.**

In the pi **bonding molecular orbital** of ethylene, the lobes that overlap in the bonding region between the nuclei are in phase; that is, they have the same sign (+ overlaps with +, and − overlaps with −). We call this reinforcement **constructive overlap.** Constructive overlap is an important feature of all bonding molecular orbitals.

In the pi **antibonding molecular orbital** (marked by *), on the other hand, lobes of opposite phase (with opposite signs, + with −) overlap in the bonding region. This **destructive overlap** causes cancelling of the wave function in the bonding region. Midway between the nuclei, this antibonding MO has a **node**: a region of zero electron density where the positive and negative phases exactly cancel.

Electrons have lower energy in the **bonding MO** than in the original p orbitals, and higher energy in the **antibonding MO.** In the ground state of ethylene, two electrons are in the bonding MO, but the antibonding MO is vacant. Stable molecules tend to have filled bonding MOs and empty antibonding MOs.

Several important principles are illustrated in Figure 11-3. Constructive overlap results in a bonding interaction; destructive overlap results in an antibonding interaction. Also, the number of pi molecular orbitals is always the same as the number of p orbitals used to form the MOs. These molecular orbitals have energies that are symmetrically distributed above and below the energy of the starting p orbitals. Half are bonding MOs, and half are antibonding MOs.

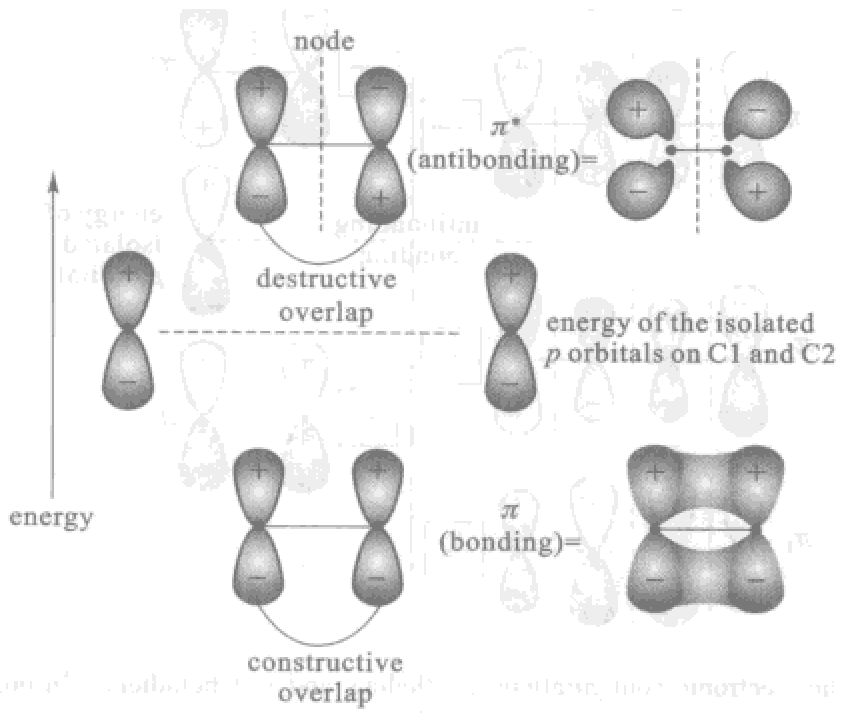
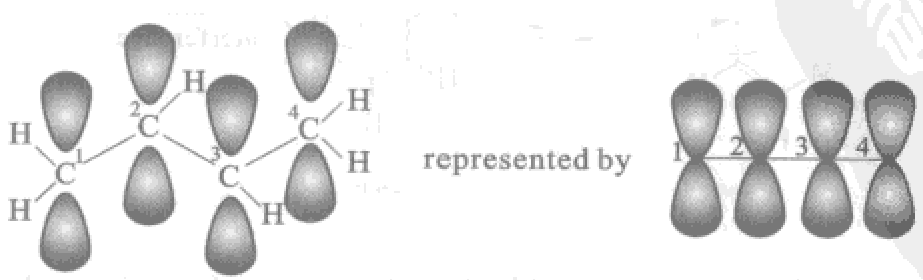


Figure 11-3 The pi molecular orbitals of ethylene. The pi bonding orbital of ethylene is formed by constructive overlap of unhybridized p orbitals on the sp^2-hybrid carbon atoms. Destructive overlap of these two orbitals forms the antibonding pi orbital. Combination of two p orbitals must give exactly two molecular orbitals.

Now we are ready to construct the molecular orbitals of 1,3-butadiene. The p orbitals on C1 through C4 overlap, giving an extended system of four p orbitals that form four pi molecular orbitals. Two MOs are bonding, and two are antibonding. To represent the four p orbitals, we draw four p orbitals in a line. Although 1,3-butadiene is not linear, this simple straight-line representation makes it easier to draw and visualize the molecular orbitals.



Butadiene has four pi electrons (two electrons in each of the two double bonds in the Lewis structure) to be placed in the four MOs. Each MO can accommodate two electrons, and the lowest-energy MOs are filled first. Therefore, the four pi electrons go into π_1 and π_2. Figure 11-4 shows the electronic configuration of 1,3-butadi-

ene. Both bonding MOs are filled, and both antibonding MOs are empty. Most stable molecules have this arrangement of filled bonding orbitals and vacant antibonding orbitals. Figure 11−4 also compares the relative energies of the ethylene MOs with the butadiene MOs to show that the conjugated butadiene system is slightly more stable than two ethylene double bonds.

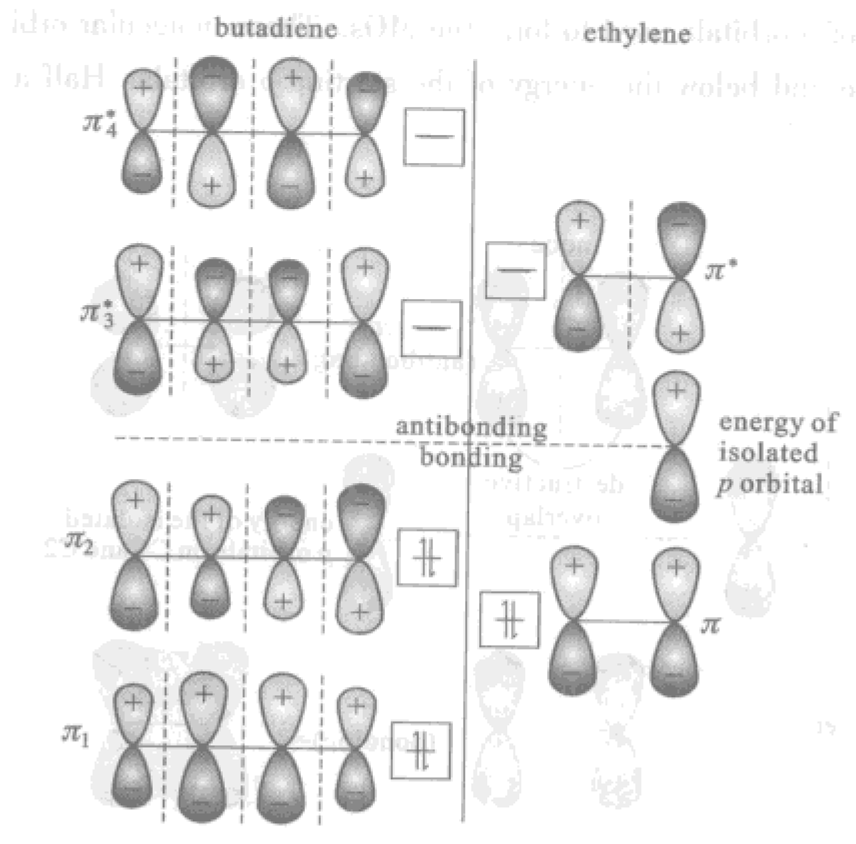
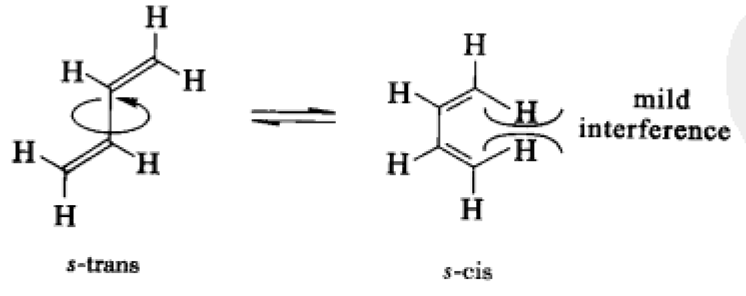


Figure 11−4 The electronic configurations of ethylene and 1,3-butadiene. In both 1,3-butadiene and ethylene, the bonding MOs are filled and the antibonding MOs are vacant. The average energy of the electrons is slightly lower in butadiene. This lower energy is the resonance stabilization of the conjugated diene.

The partial double-bond character between C2 and C3 in 1,3-butadiene explains why the molecule is most stable in a planar conformation. There are actually two planar conformations that allow overlap between C2 and C3. These conformations arise by rotation about the C2—C3 bond, and they are considered single-bond analogues of trans and cis isomers about a double bond. Thus, they are named ***s*-trans** ("single"-trans) and if ***s*-cis** ("single"-cis) **conformations.**

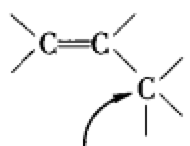


The *s*-trans conformation is 12 kJ/mol more stable than the *s*-cis conformation, which shows interference between the two nearby hydrogen atoms. The rotational barrier for these conformers (rotation about the C2—C3 bond) is only about 20 kJ/mol compared with about 250 kJ/mol for rotation of a double bond in an alkene. The *s*-cis and *s*-trans conformers of butadiene (and all the skew conformations in between) easily interconvert at room temperature.

11-4 Allylic Cations

Conjugated compounds undergo a variety of reactions, many of which involve intermediates that retain some of the resonance stabilization of the conjugated system. Common intermediates include allylic systems, particularly allylic cations and radicals. Allylic cations and radicals are stabilized by delocalization. First, we consider some reactions involving allylic cations and radicals, then (Section 11-8) we derive the molecular orbital picture of their bonding.

In Chapter 8, we saw that the $-CH_2-CH=CH_2$ group is called the **allyl group.** Many common names use this terminology.



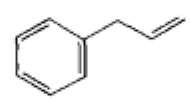
allylic position (烯丙基位)

$H_2C=CH-CH_2Br$

allyl bromide (烯丙基溴)

$H_2C=CH-CH_2OH$

allyl alcohol (烯丙基醇)

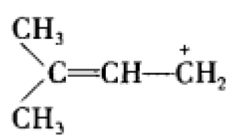


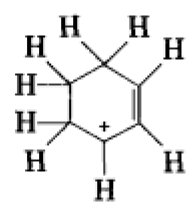
allyl benzene (烯丙基苯)

When allyl bromide is heated with a good ionizing solvent, it ionizes to the **allyl cation**, an allyl group with a positive charge. More-substituted analogues are called **allylic cations**. All allylic cations are stabilized by resonance with the adjacent double bond, which delocalizes the positive charge over two carbon atoms.

$$\underset{\text{allyl bromide}}{H_2C=CH-CH_2-\ddot{B}r:} \rightleftharpoons \underset{\text{allyl cation}}{[H_2C=CH-\overset{+}{C}H_2 \longleftrightarrow H_2\overset{+}{C}-CH=CH_2]} + :\ddot{B}r:^-$$

$H_2C=CH-\overset{+}{C}H-CH_3$





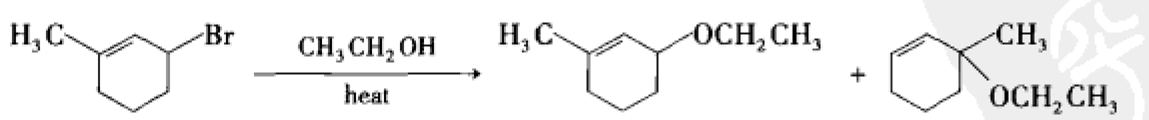
substituted allylic cations

PROBLEM 11-4

Draw another resonance form for each of the substituted allylic cations shown in the preceding figure, showing how the positive charge is shared by another carbon atom. In each case, state whether your second resonance form is a more important or less important resonance contributor than the first structure. (Which structure places the positive charge on the moresubstituted carbon atom?)

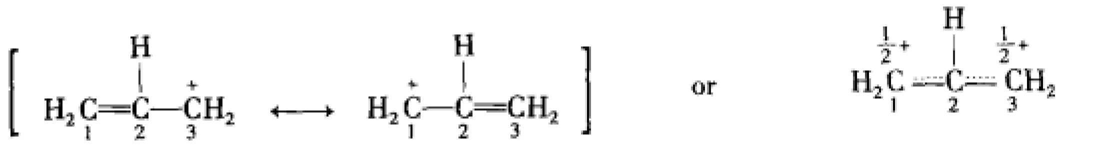
PROBLEM 11-5

When 3-bromo-1-methylcyclohexene undergoes solvolysis in hot ethanol, two products are formed. Propose a mechanism that accounts for both of these products.



We can represent a delocalized ion such as the allyl cation either by resonance forms, as shown on the left in the following figure, or by a combined structure, as shown on the right. Although the combined structure is more concise, it is sometimes confusing because it attempts to convey all the information provided by two or more

resonance forms.

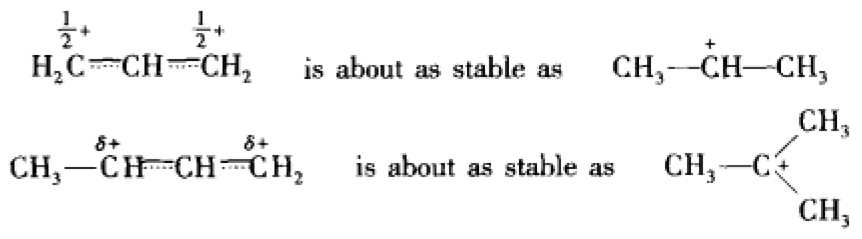


resonance forms   combined representation

Because of its resonance stabilization, the (primary) allyl cation is about as stable as a simple secondary carbocation, such as the isopropyl cation. Substituted allylic cations generally have at least one secondary carbon atom bearing part of the positive charge; they are about as stable as simple tertiary carbocations such as the *t*-butyl cation.

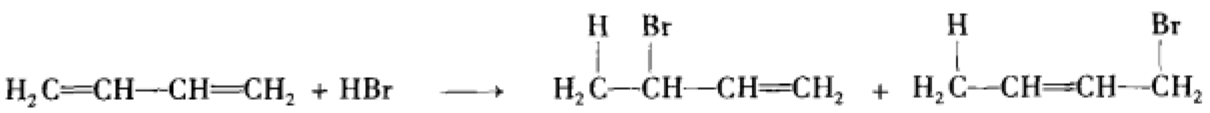
Stability of carbocations

$$H_3C^+ < 1° < 2°,\ \text{allyl} < 3°,\ \text{substituted allylic}$$



11–5 1,2-and 1,4-Addition to Conjugated Dienes

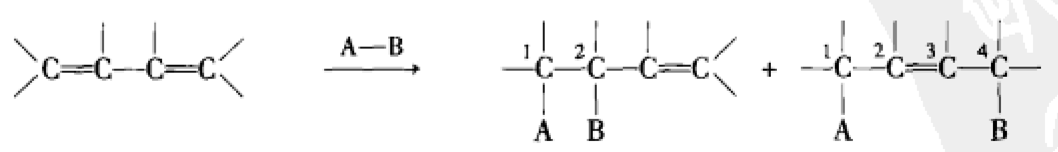
Electrophilic additions to conjugated dienes usually involve allylic cations as intermediates. Unlike simple carbocations, an allylic cation can react with a nucleophile at either of its positive centers. Let's consider the addition of HBr to 1,3-butadiene, an electrophilic addition that produces a mixture of two constitutional isomers. One product, 3-bromo-1-butene, results from Markovnikov addition across one of the double bonds. In the other product, 1-bromo-2-butene, the double bond shifts to the C2—C3 position.



3-bromo-1-butene   1-bromo-2-butene

1,2-addition   1,4-addition

The first product results from electrophilic addition of HBr across a double bond. This process is called a **1,2-addition** whether or not these two carbon atoms are numbered 1 and 2 in naming the compound. In the second product, the proton and bromide ion add at the ends of the conjugated system to carbon atoms with a 1,4-relationship. Such an addition is called a **1,4-addition** whether or not these carbon atoms are numbered 1 and 4 in naming the compound.

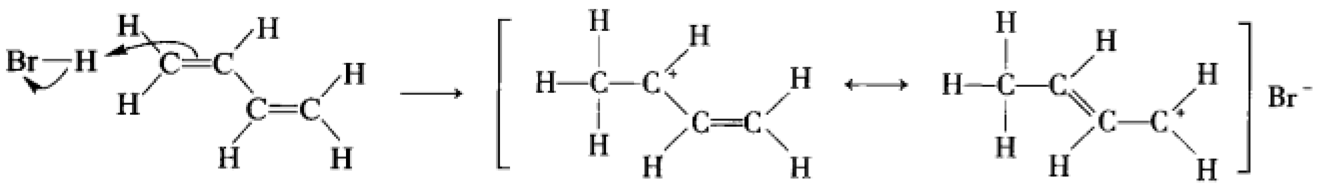


1,2-addition   1,4-addition

The mechanism is similar to other electrophilic additions to alkenes. The proton is the electrophile, adding to the alkene to give the most stable carbocation. Protonation of 1,3-butadiene gives an allylic cation, which is stabilized by resonance delocalization of the positive charge over two carbon atoms. Bromide can attack this resonance-stabilized intermediate at either of the two carbon atoms sharing the positive charge. Attack at the secondary carbon gives 1,2-addition; attack at the primary carbon gives 1,4-addition.

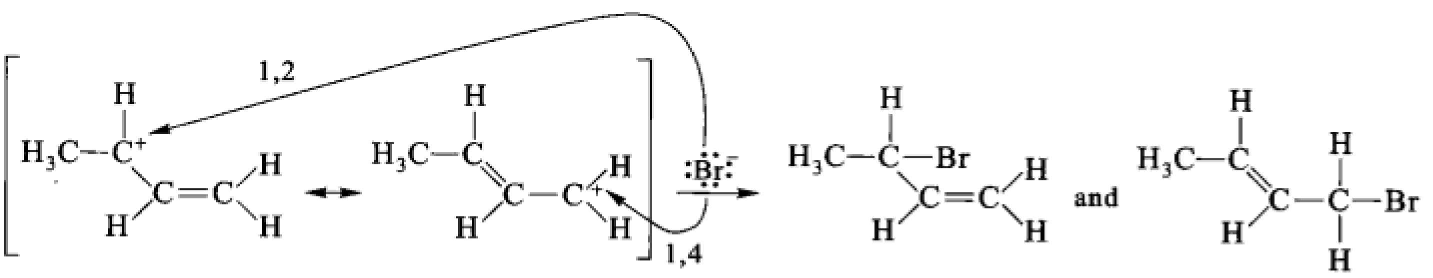
MECHANISM 11-1 1,2-and 1,4-Addition to a Conjugated Diene

***Step 1*:** Protonation of one of the double bonds forms a resonance-stabilized allylic cation.



allylic cation (烯丙基碳正离子)

***Step 2*:** A nucleophile attacks at either electrophilic carbon atom.



1,2-addition 1,4-addition

The key to formation of these two products is the presence of a double bond in position to form a stabilized allylic cation. Molecules having such double bonds are likely to react via resonance-stabilized intermediates.

PROBLEM 11-6

Treatment of an alkyl halide with alcoholic $AgNO_3$ often promotes ionization.

$$Ag^+ + R{-}Cl \longrightarrow AgCl + R^+$$

When 3-chloro-l-methylcyclopentene reacts with $AgNO_3$ in ethanol, two isomeric ethers are formed. Suggest structures, and propose a mechanism for their formation.

PROBLEM 11-7

Propose a mechanism for each reaction, showing explicitly how the observed mixtures of products are formed.

(a) 3-methyl-2-buten-1-ol + HBr ⟶ 1-bromo-3-methyl-2-butene + 3-bromo-3-methyl-1-butene

(b) 2-methyl-3-buten-2-ol + HBr ⟶ 1-bromo-3-methyl-2-butene + 3-bromo-3-methyl-1-butene

(c) 1,3-butadiene + Br_2 ⟶ 3,4-dibromo-1-butene + 1,4-dibromo-2-butene

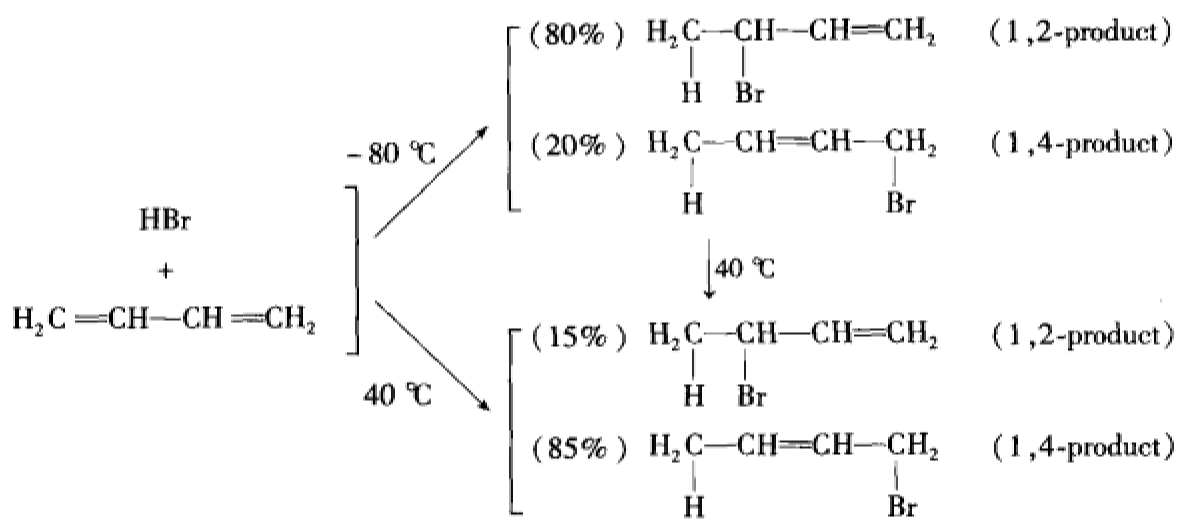
(d) 1-chloro-2-butene + $AgNO_3$, H_2O ⟶ 2-buten-1-ol + 3-buten-2-ol

(e) 3-chloro-1-butene + $AgNO_3$, H_2O ⟶ 2-buten-1-ol + 3-buten-2-ol

11-6 Kinetic versus Thermodynamic Control in the Addition of HBr to 1,3-Butadiene

One of the interesting peculiarities of the reaction of 1,3-butadiene with HBr is the effect of temperature on the

products. If the reagents are allowed to react briefly at −80 ℃, the 1,2-addition product predominates. If this reaction mixture is later allowed to warm to 40 ℃, however, or if the original reaction is carried out at 40 ℃, the composition favors the 1,4-addition product.



This variation in product composition reminds us that the most stable product is not always the major product. Of the two products, we expect 1-bromo-2-butene (the 1,4-product) to be more stable, since it has the more substituted double bond. This prediction is supported by the fact that this isomer predominates when the reaction mixture is warmed to 40 ℃ and allowed to equilibrate.

A reaction-energy diagram for the second step of this reaction (Figure 11−5) helps to show why one product is favored at low temperatures and another at higher temperatures. The allylic cation is in the center of the diagram; it can react toward the left to give the 1,2-product or toward the right to give the 1,4-product. The initial product depends on where bromide attacks the resonance-stabilized allylic cation. Bromide can attack at either of the two carbon atoms that share the positive charge. Attack at the secondary carbon gives 1,2-addition, and attack at the primary carbon gives 1,4-addition.

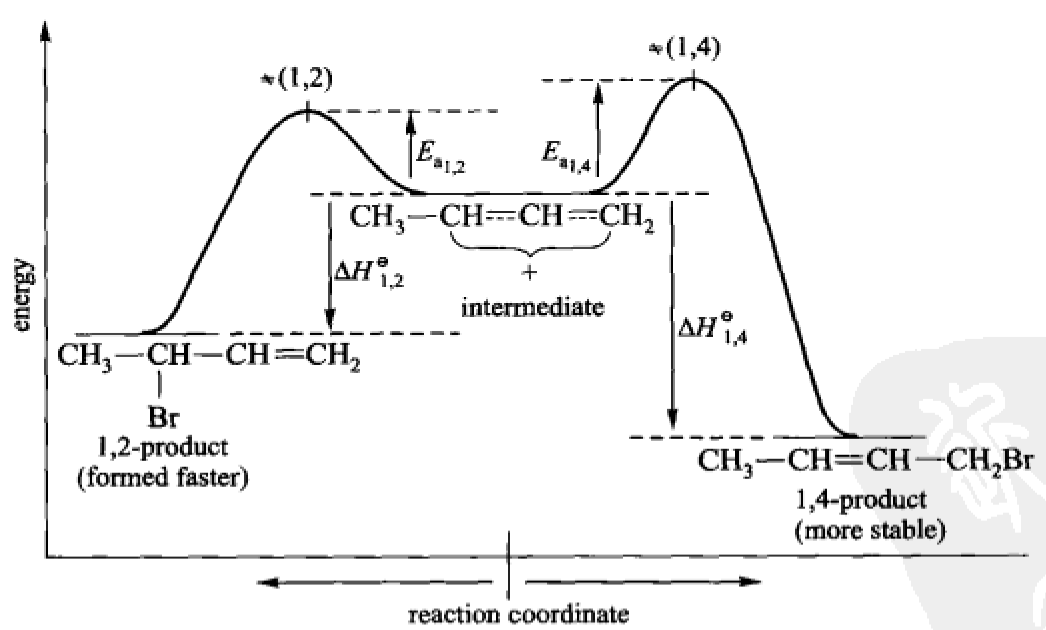
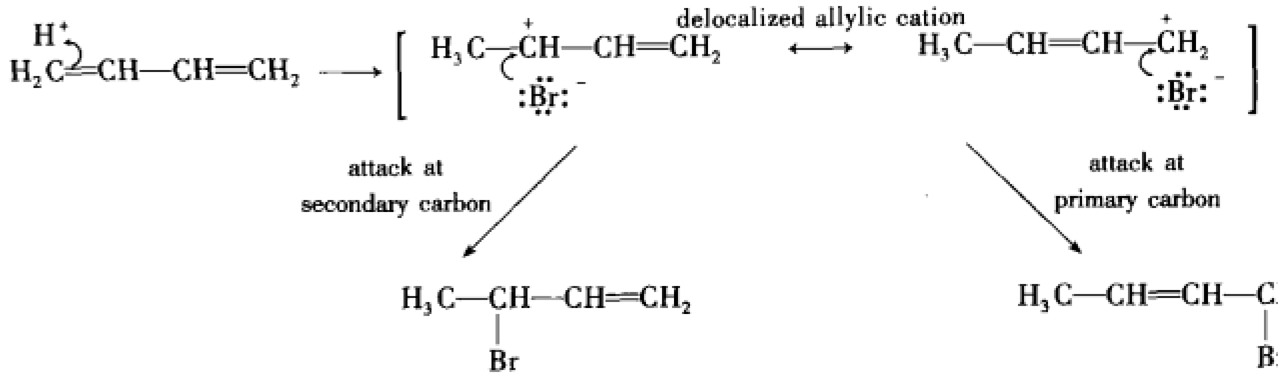


Figure 11−5 Reaction-energy diagram for the second step of the addition of 1,3 butadiene to HBr. The allylic carbocation (center) can react at either of its electrophilic carbon atoms. The transition state (‡) leading to 1,2-addition has a lower energy than that leading to the 1,4 product, so the 1,2-product is formed faster (kinetic product). The 1,2-product is not as stable as the 1,4-product, however. If equilibrium is reached, the 1,4-product predominates (thermodynamic product).



Kinetic Control at −80 ℃ The transition state for 1,2-addition has a lower energy than the transition state for 1,4-addition, giving the 1,2-addition a lower activation energy (E_a). This is not surprising, because 1,2-addition results from bromide attack at the more substituted secondary carbon, which bears more of the positive charge because it is better stabilized than the primary carbon. Because the 1,2-addition has a lower activation energy than the 1,4-addition, the 1,2-addition takes place faster (at *all* temperatures).

Attack by bromide on the allylic cation is a strongly exothermic process, so the reverse reaction has a large activation energy. At −80 ℃, few collisions take place with this much energy, and the rate of the reverse reaction is practically zero. Under these conditions, the product that is formed faster predominates. Because the kinetics of the reaction determine the results, this situation is called **kinetic control** of the reaction. The 1,2-product, favored under these conditions, is called the **kinetic product.**

Thermodynamic Control at 40 ℃ At 40 ℃, a significant fraction of molecular collisions have enough energy for reverse reactions to occur. Notice that the activation energy for the reverse of the 1,2-addition is less than that for the reverse of the 1,4-addition. Although the 1,2-product is still formed faster, it also reverts to the allylic cation faster than the 1,4-product does. At 40 ℃, an equilibrium is set up, and the relative energy of each species determines its concentration. The 1,4-product is the most stable species, and it predominates. Since thermodynamics determine the results, this situation is called **thermodynamic control** (or **equilibrium control**) of the reaction. The 1,4-product, favored under these conditions, is called the **thermodynamic product.**

We will see many additional reactions whose products may be determined by kinetic control or by thermodynamic control, depending on the conditions. In general, reactions that do not reverse easily are kinetically controlled because an equilibrium is rarely established. In kinetically controlled reactions, the product with the lowest-energy transition state predominates. Reactions that are easily reversible are thermodynamically controlled unless something happens to prevent equilibrium from being attained. In thermodynamically controlled reactions, the lowest-energy product predominates.

PROBLEM 11-8

When Br_2 is added to 1,3-butadiene at −15 ℃, the product mixture contains 60% of product A and 40% of product B. When the same reaction takes place at 60 ℃, the product ratio is 10% A and 90% B.

(a) Propose structures for products A and B. (*Hint*: In many cases, an allylic carbocation is more stable than a bromonium ion.)

(b) Propose a mechanism to account for formation of both A and B.

(c) Show why A predominates at −15 ℃, but B predominates at 60 ℃.

(d) If you had a solution of pure A, and its temperature was raised to 60 ℃, what would you expect to happen? Propose a mechanism to support your prediction.

11 – 7 Allylic Radicals

Like allylic cations, allylic radicals are stabilized by resonance delocalization. For example, the mechanism of free-radical bromination of cyclohexene is shown next. Substitution occurs entirely at the allylic position, where abstraction of a hydrogen gives a resonance-stabilized allylic radical as the intermediate.

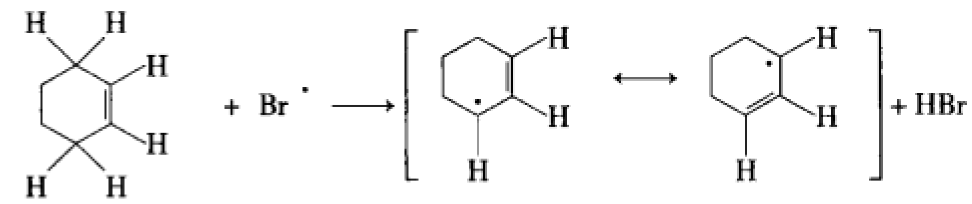
MECHANISM 11 – 2 Free-Radical Allylic Bromination

***Initiation*:** Formation of radicals.

$$Br_2 \xrightarrow{h\nu} 2Br\cdot$$

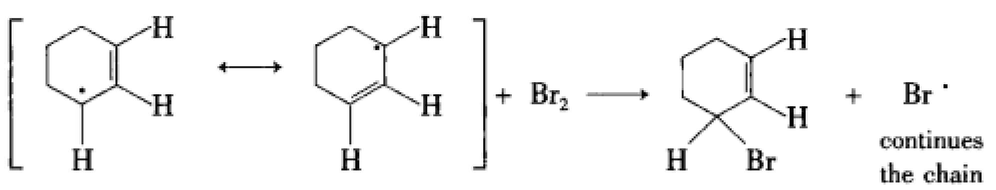
***Propagation*:** Each step consumes a radical and forms another radical leading to products.

***First Propagation Step*:** The bromine radical abstracts an allylic hydrogen to produce an allylic radical.



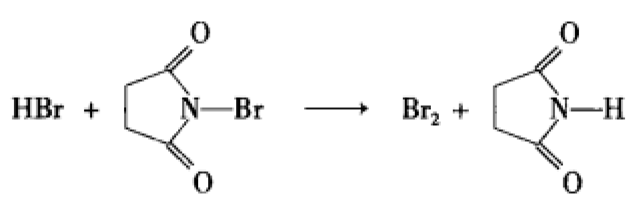
allylic hydrogens (烯丙基氢) an allylic radical (烯丙基自由基)

***Second Propagation Step*:** The allylic radical in turn reacts with a bromine molecule to form an allyl bromide and a new bromine atom, which continues the chain.



allylic radical allylic bromide

***Regeneration of Br$_2$*:** NBS reacts with HBr to regenerate the molecule of bromine used in the allylic bromination step.



N-bromosuccinimide (NBS) (*N*-溴丁二酰亚胺) succinimide (丁二酰亚胺)

Stability of Allylic Radicals Why is it that (in the first propagation step) a bromine radical abstracts only an allylic hydrogen atom, and not one from another secondary site? Abstraction of allylic hydrogens is preferred because the allylic free radical that results is resonance-stabilized. The bond-dissociation enthalpies required to generate several free radicals are compared next. Notice that the allyl radical (a primary free radical) is actually 13 kJ/mol *more* stable than the tertiary butyl radical.

$$CH_3CH_2{-}H \longrightarrow CH_3CH_2\cdot + H\cdot \qquad \Delta H^{\ominus} = +410 \text{ kJ/mol (primary)}$$

$$(CH_3)_2CH{-}H \longrightarrow (CH_3)_2CH\cdot + H\cdot \qquad \Delta H^{\ominus} = +393 \text{ kJ/mol (secondary)}$$

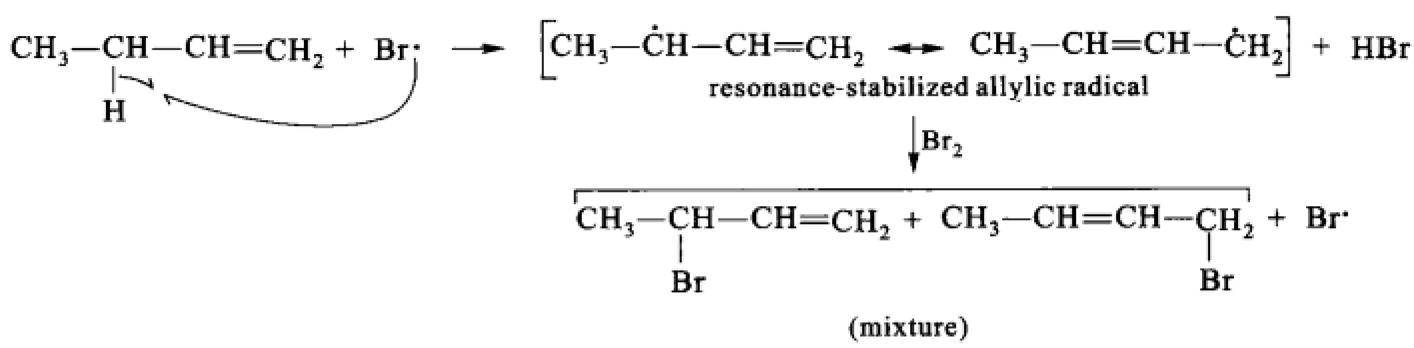
$$(CH_3)_3C{-}H \longrightarrow (CH_3)_3C\cdot + H\cdot \qquad \Delta H^{\ominus} = +381 \text{ kJ/mol (tertiary)}$$

$$H_2C{=}CH{-}CH_2{-}H \longrightarrow H_2C{=}CH{-}CH_2\cdot + H\cdot \qquad \Delta H^{\ominus} = +368 \text{ kJ/mol (allyl)}$$

The allylic 2-cyclohexenyl radical has its unpaired electron delocalized over two secondary carbon atoms, so

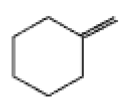
it is even more stable than the unsubstituted allyl radical. The second propagation step may occur at either of the radical carbons, but in this symmetrical case, either position gives 3-bromocyclohexene as the product. Less-symmetrical compounds often give mixtures of products resulting from an **allylic shift**: In the product, the double bond can appear at either of the positions it occupies in the resonance forms of the allylic radical. An allylic shift in a radical reaction is similar to the 1,4-addition of an electrophilic reagent such as HBr to a diene (Section 11−5).

The following propagation steps show how a mixture of products results from the free-radical allylic bromination of 1-butene.



PROBLEM 11−9

When methylenecyclohexane is treated with a low concentration of bromine under irradiation by a sunlamp, two substitution products are formed.

 $+ Br_2 \longrightarrow$ two substitution products + HBr

methylenecyclohexane (亚甲基环己烷)

(**a**) Propose structures for these two products.

(**b**) Propose a mechanism to account for their formation.

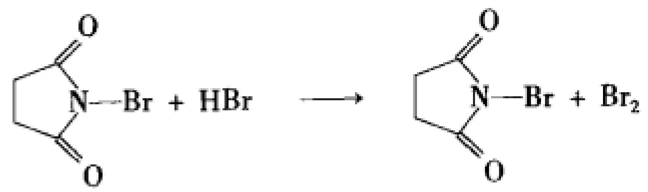
Bromination Using NBS At higher concentrations, bromine *adds* across double bonds (via a bromonium ion) to give saturated dibromides (Section 9−8). In the allylic bromination just shown, bromine *substitutes* for a hydrogen atom. The key to getting substitution is to have a low concentration of bromine, together with light or free radicals to initiate the reaction. Free radicals are highly reactive, and even a small concentration of radicals can produce a fast chain reaction.

Simply adding bromine might make the concentration too high, resulting in ionic addition of bromine across the double bond. A convenient bromine source for allylic bromination is *N*-bromosuccinimide (NBS), a brominated derivative of succinimide. Succinimide is a cyclic amide of the four-carbon diacid succinic acid. NBS provides a fairly constant, low concentration of Br_2 because it reacts with HBr liberated in the substitution, converting it back into Br_2. This reaction also removes the HBr byproduct, preventing it from adding across the double bond by its own free-radical chain reaction.

Step 1: Free-radical allylic substitution

$$R\text{—}H + Br_2 \xrightarrow{h\nu} R\text{—}Br + HBr$$

Step 2: NBS converts the HBr byproduct back into Br_2

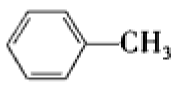


NBS succinimide

The NBS reaction is carried out in a clever way. The allylic compound is dissolved in carbon tetrachloride, and one equivalent of NBS is added. NBS is denser than CCl_4 and not very soluble in it, so it sinks to the bottom of the CCl_4 solution. The reaction is initiated using a sunlamp for illumination or a radical initiator such as a peroxide. The NBS gradually *appears* to rise to the top of the CCl_4 layer. It is actually converted to succinimide, which is less dense than CCl_4. Once all the solid succinimide has risen to the top, the sunlamp is turned off, the solution is filtered to remove the succinimide, and the CCl_4 is evaporated to recover the product.

PROBLEM 11-10

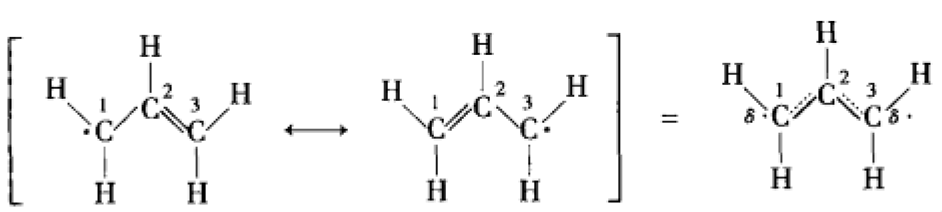
Predict the product(s) of light-initiated reaction with NBS in CCl_4 for the following starting materials.

(a) cyclopentene **(b)** *trans*-2-pentene **(c)** 

toluene (甲苯)

11-8 Molecular Orbitals of the Allylic System

Let's take a closer look at the electronic structure of allylic systems, using the allyl radical as our example. One resonance form shows a pi bond between C2 and C3 with the radical electron on C1, and the other shows a pi bond between C1 and C2 with the radical electron on C3. These two resonance forms imply that there is half a pi bond between C1 and C2 and half a pi bond between C2 and C3, with the radical electron half on C1 and half on C3.



resonance forms combined representation

Remember that no resonance form has an independent existence: A compound has characteristics of all its resonance forms at the same time, but it does not "resonate" among them. The *p* orbitals of all three carbon atoms must be parallel to have pi bonding overlap simultaneously between C1 and C2 and between C2 and C3. The geometric structure of the allyl system is shown in Figure 11-6. The allyl cation, the allyl radical, and the allyl anion all have this same geometric structure, differing only in the number of pi electrons.

Just as the four *p* orbitals of 1,3-butadiene overlap to form four molecular orbitals, the three atomic *p* orbitals of the allyl system overlap to form three molecular orbitals, shown in Figure 11-7. These three MOs share several important features with the MOs of the butadiene system. The first MO is entirely bonding, the second has one node, and the third has two nodes and (because it is the highest-energy MO) is entirely antibonding.

As with butadiene, we expect that half of the MOs will be bonding, and half antibonding; but with an odd number of MOs, they cannot be symmetrically divided. One of the MOs must appear at the middle of the energy

levels, neither bonding nor antibonding: It is a **nonbonding molecular orbital**. Electrons in a nonbonding orbital have the same energy as in an isolated p orbital.

The structure of the nonbonding orbital (π_2) may seem strange because there is zero electron density on the center p orbital (C2). This is the case because π_2 must have one node, and the only symmetrical position for one node is in the center of the molecule, crossing C2. We can tell from its structure that π_2 must be nonbonding, because C1 and C3 both have zero overlap with C2. The total is zero bonding, or a nonbonding orbital.

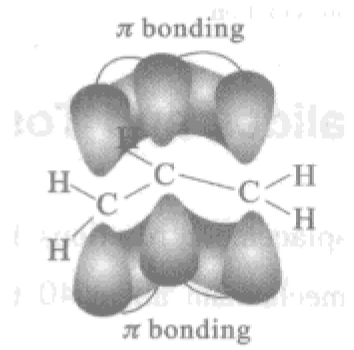


Figure 11-6 Geometric structure of the allyl cation, allyl radical, and allyl anion.

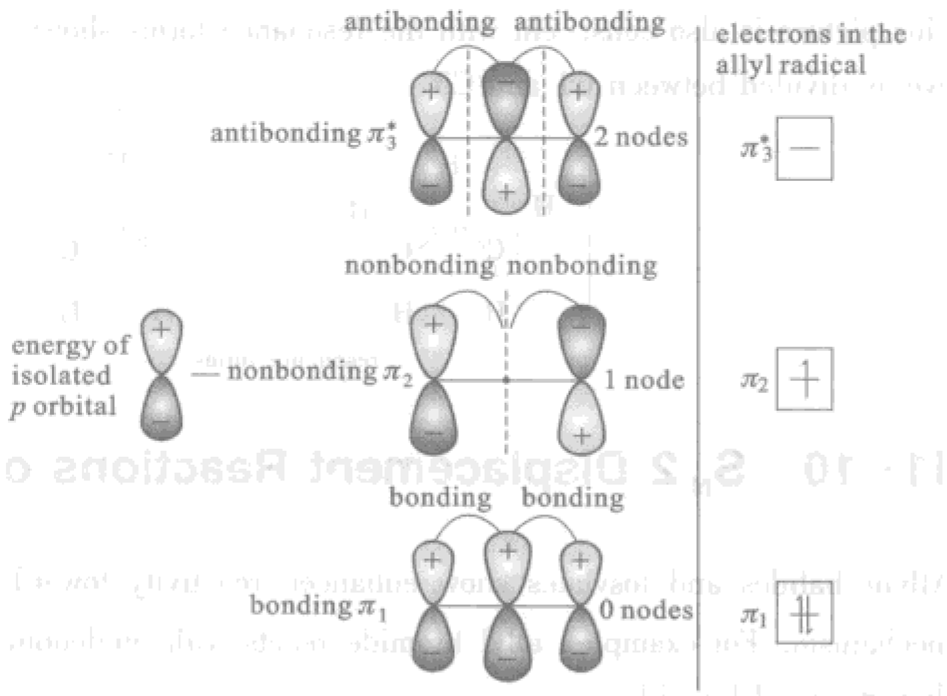


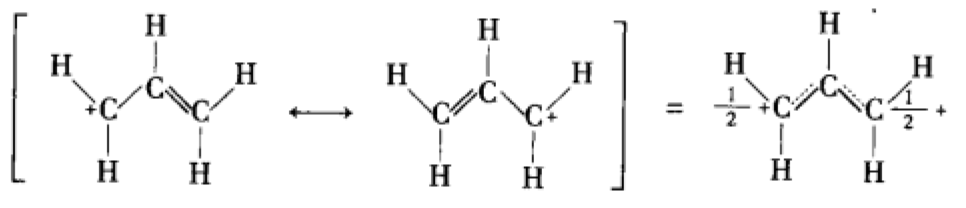
Figure 11-7 The three molecular orbitals of the allyl system. The lowest-energy MO (π_1) has no nodes and is entirely bonding. The intermediate orbital (π_2) is nonbonding, having one symmetrical node that coincides with the center carbon atom. The highest-energy MO (π_3^*) has two nodes and is entirely antibonding. In the allyl radical, π_1 is filled. The unpaired electron is in π_2, having its electron density entirely on C1 and C3.

11-9 Electronic Configurations of the Allyl Radical, Cation, and Anion

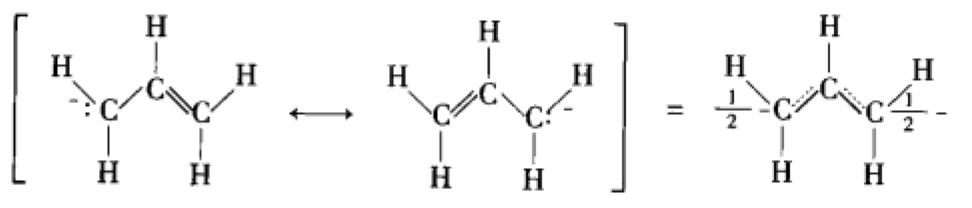
Figure 11-7 shows the electronic structure for the allyl radical, with three pi electrons in the lowest available molecular orbitals. Two electrons are in the all-bonding MO (π_1), representing the pi bond shared between the C1—C2 bond and the C2—C3 bond. The unpaired electron goes into π_2 with zero electron density on the center carbon atom (C2). This MO representation agrees with the resonance picture showing the radical electron shared equally by C1 and C3, but not C2. Both the resonance and MO pictures successfully predict that the radical will react at either of the end carbon atoms, C1 or C3.

The electronic configuration of the allyl cation differs from that of the allyl radical; it lacks the unpaired electron in π_2, which has half of its electron density on C1 and half on C3. In effect, we have removed half an electron from each of C1 and C3, while C2 remains unchanged. This MO picture is consistent with the resonance

picture showing the positive charge shared by C1 and C3.



The molecular orbital representation shows the allyl anion with a pair of electrons in π_2, a nonbonding orbital. This picture is also consistent with the resonance forms shown earlier, with a lone pair of nonbonding electrons evenly divided between C1 and C3.



11-10 S_N2 Displacement Reactions of Allylic Halides and Tosylates

Allylic halides and tosylates show enhanced reactivity toward nucleophilic displacement reactions by the S_N2 mechanism. For example, allyl bromide reacts with nucleophiles by the S_N2 mechanism about 40 times faster than *n*-propyl bromide.

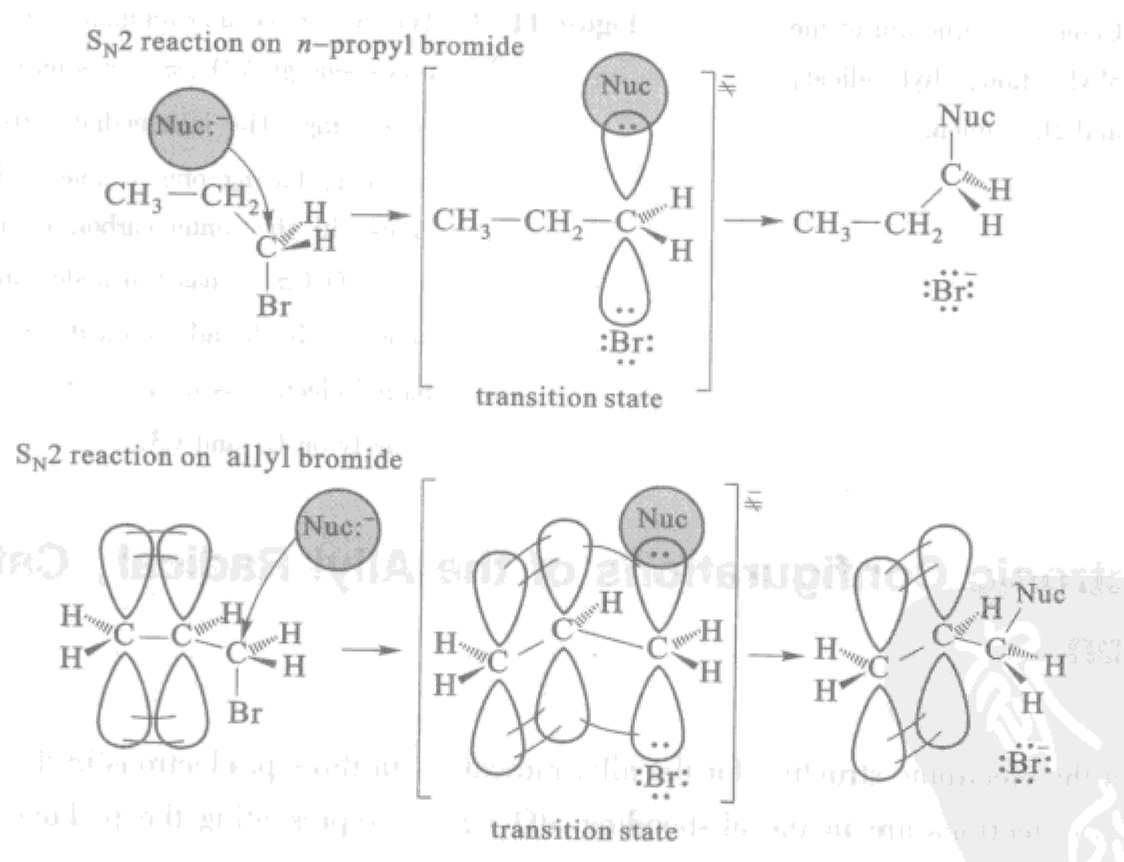


Figure 11-8 Allylic delocalization in the S_N2 transition state. The transition state for the S_N2 reaction of allyl bromide with a nucleophile is stabilized by conjugation of the double bond with the *p* orbital that is momentarily present on the reacting carbon atom. The resulting overlap lowers the energy of the transition state, increasing the reaction rate.

Figure 11-8 shows how this rate enhancement can be explained by allylic delocalization of electrons in the transition state. The transition state for the S_N2 reaction looks like a trigonal carbon atom with a *p* orbital perpen-

dicular to the three substituents. The electrons of the attacking nucleophile are forming a bond using one lobe of the *p* orbital while the leaving group's electrons are leaving from the other lobe.

When the substrate is allylic, the transition state receives resonance stabilization through conjugation with the *p* orbitals of the pi bond. This stabilization lowers the energy of the transition state, resulting in a lower activation energy and an enhanced rate.

The enhanced reactivity of allylic halides and tosylates makes them particularly attractive as electrophiles for S_N2 reactions. Allylic halides are so reactive that they couple with Grignard and organolithium reagents, a reaction that does not work well with unactivated halides.

$$H_2C{=}CH{-}CH_2Br + CH_3{-}(CH_2)_3{-}Li \longrightarrow H_2C{=}CH{-}CH_2{-}(CH_2)_3{-}CH_3 + LiBr$$

allyl bromide — *n*-butylithium（正丁基锂） — 1-heptene (85%)

11-11 The Diels-Alder Reaction

In 1928, German chemists Otto Diels and Kurt Alder discovered that alkynes and alkenes with electron-withdrawing groups add to conjugated dienes to form six-membered rings. The **Diels-Alder reaction** has proven to be a useful synthetic tool, providing one of the best ways to make six-membered rings with diverse functionality and controlled stereochemistry. Diels and Alder were awarded the Nobel Prize in 1950 for their work.

The Diels-Alder reaction is also called a [**4+2**] **cycloaddition** because a ring is formed by the interaction of four pi electrons in the diene with two pi electrons of the alkene or alkyne. Since the electron-poor alkene or alkyne is prone to react with a diene, it is called a **dienophile**. In effect, the Diels-Alder reaction converts two pi bonds into two sigma bonds. We can symbolize the Diels-Alder reaction by using three arrows to show the movement of three pairs of electrons. This electron movement is **concerted**, with three pairs of electrons moving simultaneously. The electron-withdrawing groups (—W) are usually carbonyl-containing (C=O) groups or cyano (—C≡N) groups.

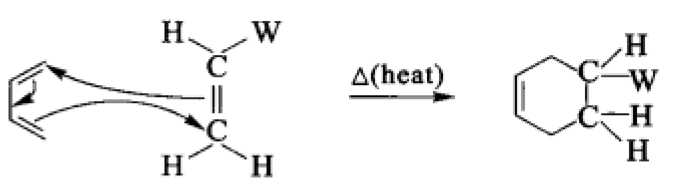
The Diels-Alder reaction is like a nucleophile-electrophile reaction. The diene is electron-rich, and the dienophile is electron-poor. Simple dienes such as 1,3-butadiene are sufficiently electron-rich to be effective dienes for the Diels-Alder reaction. The presence of electron-releasing groups such as alkyl groups or alkoxy (—OR) groups may further enhance the reactivity of the diene.

Simple alkenes and alkynes such as ethene and ethyne are poor dienophiles, however. A good dienophile generally has one or more electron-withdrawing groups (—W) pulling electron density away from the pi bond. Dienophiles commonly have carbonyl-containing (C=O) groups or cyano (—C≡N) groups to enhance their Diels-Alder reactivity.

KEY MECHANISM 11-3 The Diels-Alder Reaction

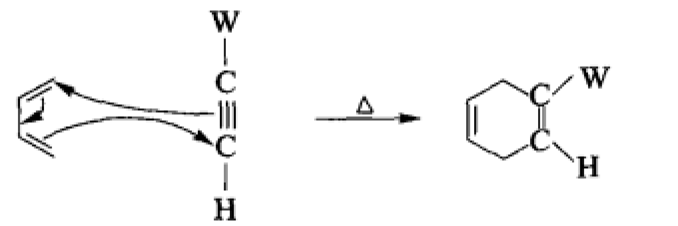
The Diels-Alder is a one-step, concerted mechanism.

A diene reacts with an electron-poor alkene to give a new cyclohexene ring.



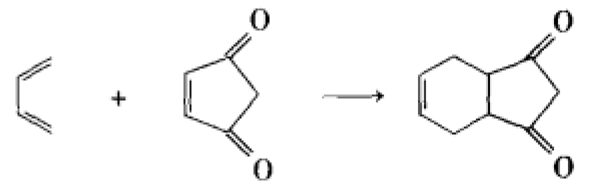
diene（双烯体） electron-rich — dienophile（亲双烯体） electron-poor — a cyclohexene ring

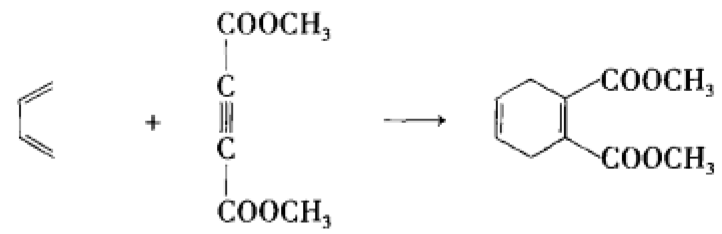
A diene reacts with an electron-poor alkyne to give a cyclohexadiene.



diene dienophile a cyclohexa-1,4-diene ring

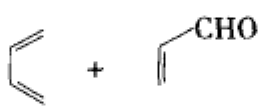
Example

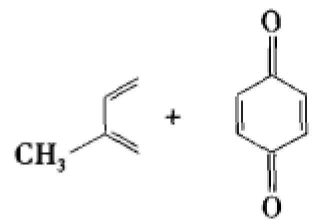


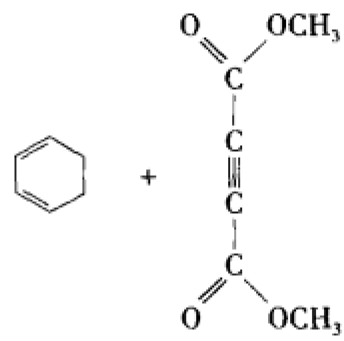


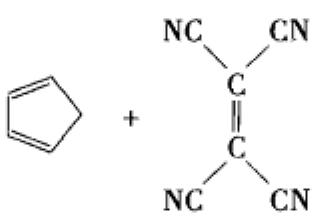
PROBLEM 11-11

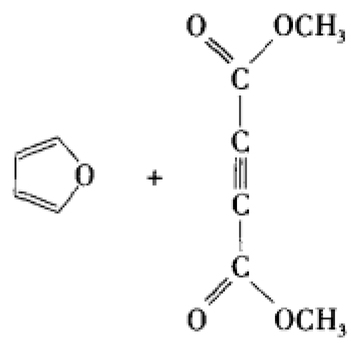
Predict the products of the following proposed Diels-Alder reactions.

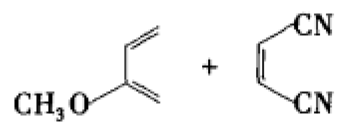
(a) 

(b) 

(c) 

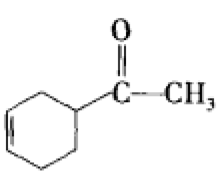
(d) 

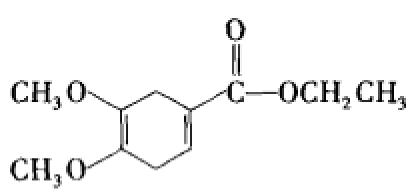
(e) 

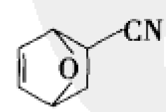
(f) 

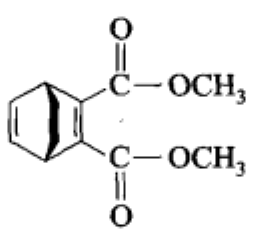
PROBLEM 11-12

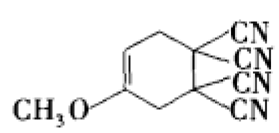
What dienes and dienophiles would react to give the following Diels-Alder products?

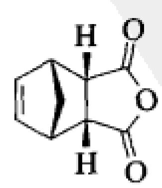
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

11−11A Stereochemical Requirements of the Diels-Alder Transition State

The mechanism of the Diels-Alder reaction is a concerted cyclic movement of six electrons: four in the diene and two in the dienophile. For the three pairs of electrons to move simultaneously, the transition state must have a geometry that allows overlap of the two end *p* orbitals of the diene with those of the dienophile. Figure 11−9 shows the required geometry of the transition state. The geometry of the Diels-Alder transition state explains why some isomers react differently from others, and it enables us to predict the stereochemistry of the products.

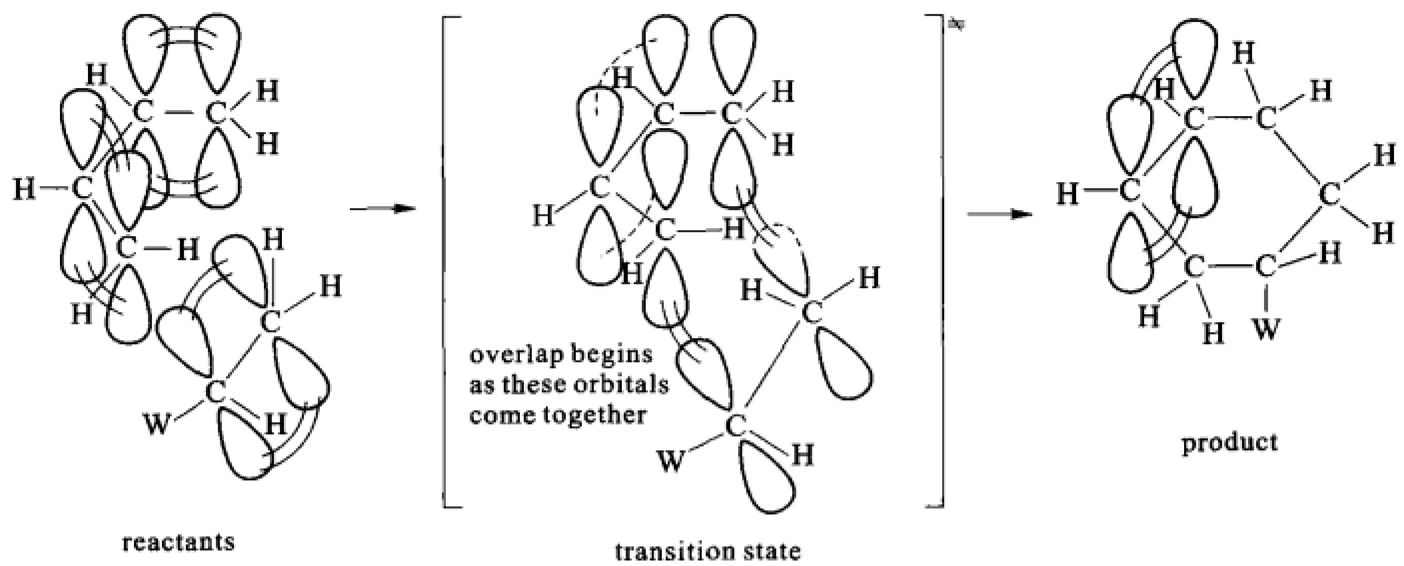
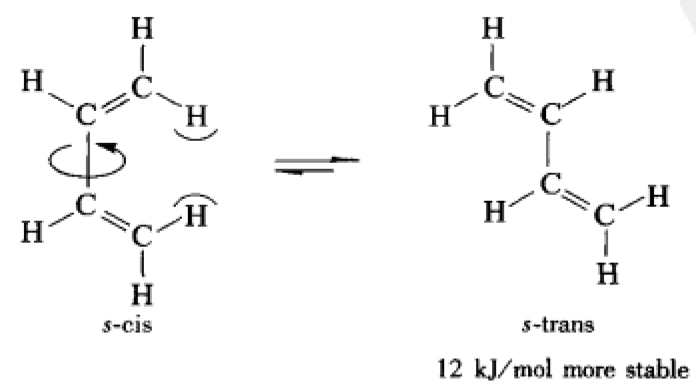


Figure 11−9 The geometry of the Diels-Alder transition state. The Diels-Alder reaction has a concerted mechanism, with all the bond making and bond breaking occurring in a single step. Three pairs of electrons move simultaneously, requiring a transition state with overlap between the end *p* orbitals of the diene and those of the dienophile.

Three stereochemical features of the Diels-Alder reaction are controlled by the requirements of the transition state:

***s*-cis Conformation of the Diene** The diene must be in the *s*-cis conformation to react. When the diene is in the *s*-trans conformation, the end *p* orbitals are too far apart to overlap with the *p* orbitals of the dienophile. The *s*-trans conformation usually has a lower energy than the *s*-cis, but this energy difference is not enough to prevent most dienes from undergoing Diels-Alder reactions. For example, the *s*-trans conformation of butadiene is only 9.6 kJ/mol lower in energy than the *s*-cis conformation.



Structural features that aid or hinder the diene in achieving the *s*-cis conformation affect its ability to participate in Diels-Alder reactions. Figure 11−10 shows that dienes with functional groups that hinder the *s*-cis conformation react more slowly than butadiene. Dienes with functional groups that hinder the *s*-trans conformation react faster than butadiene.

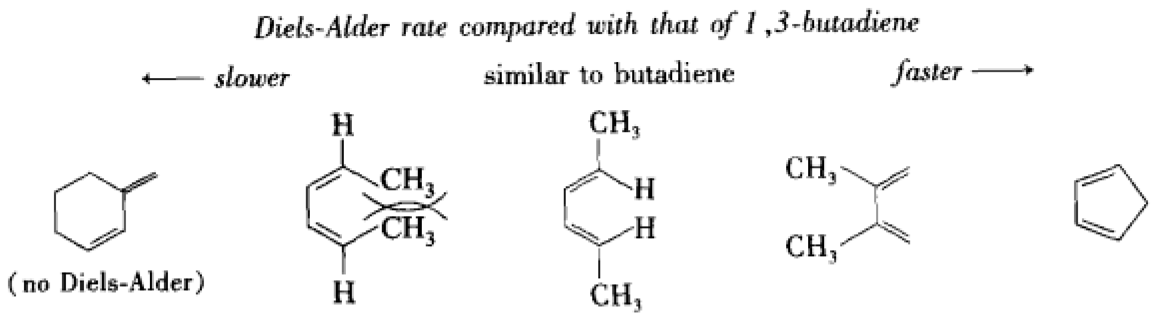
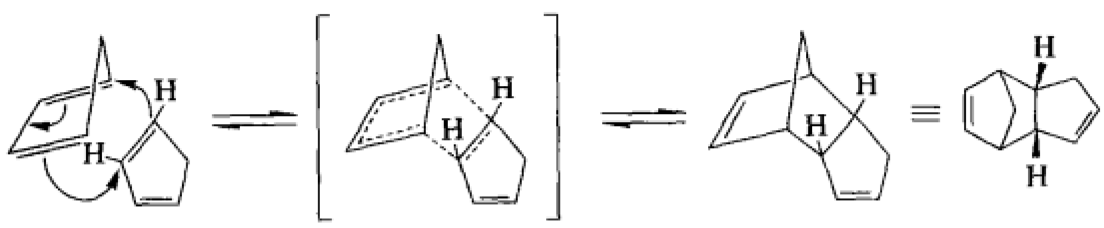
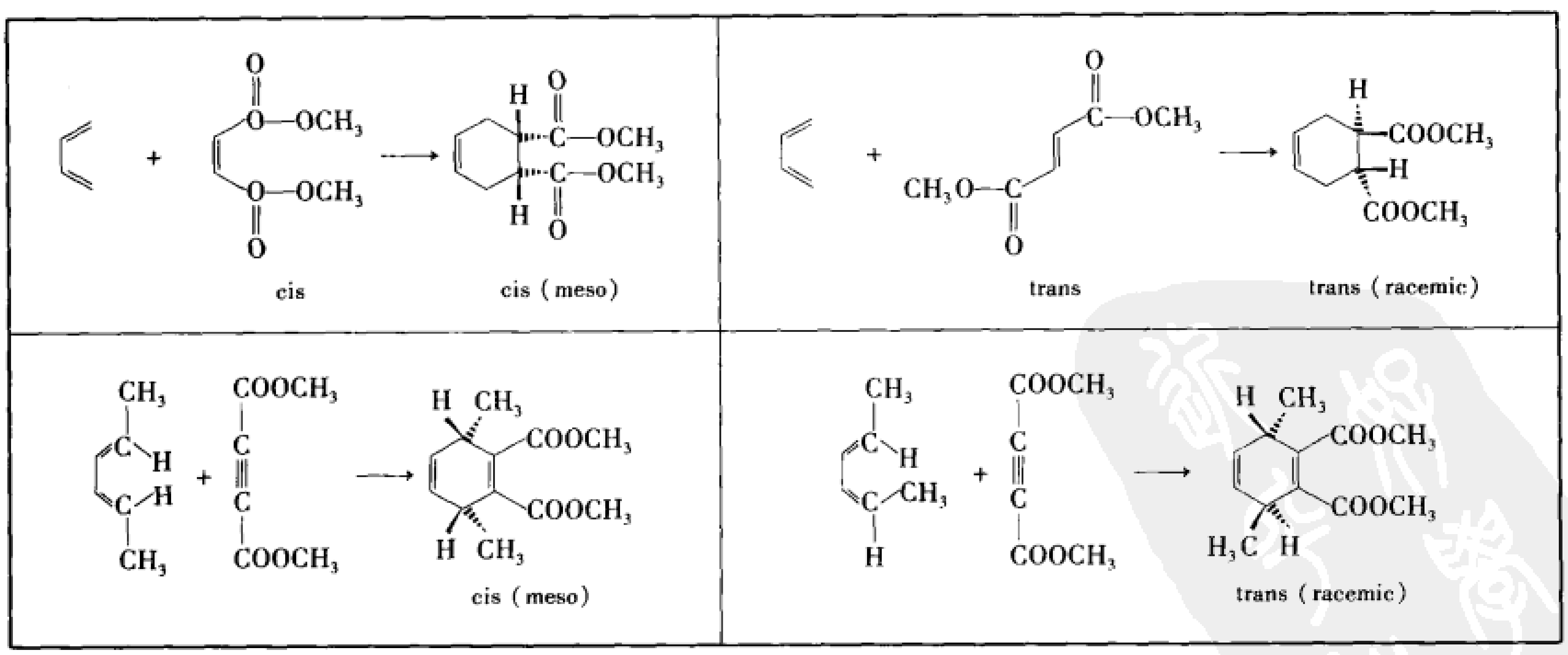


Figure 11-10 Dienes that easily adopt the *s*-cis conformation undergo the Diels-Alder reaction more readily.

Because cyclopentadiene is fixed in the *s*-cis conformation, it is highly reactive in the Diels-Alder reaction. It is so reactive, in fact, that at room temperature, cyclopentadiene slowly reacts with itself to form dicyclopentadiene. Cyclopentadiene is regenerated by heating the dimer above 200 ℃. At this temperature, the Diels-Alder reaction reverses, and the more volatile cyclopentadiene monomer distills over into a cold flask. The monomer can be stored indefinitely at dry-ice temperatures.



Syn Stereochemistry The Diels-Alder reaction is a syn addition with respect to both the diene and the dienophile. The dienophile adds to one face of the diene, and the diene adds to one face of the dienophile. As you can see from the transition state in Figure 11-9, there is no opportunity for any of the substituents to change their stereochemical positions during the course of the reaction. Substituents that are on the same side of the diene or dienophile will be cis on the newly formed ring. The following examples show the results of this syn addition.



The Endo Rule When the dienophile has a pi bond in its electron-withdrawing group (as in a carbonyl group or a cyano group), the *p* orbitals in that electron-withdrawing group approach one of the central carbon atoms (C2 or C3) of the diene. This proximity results in **secondary overlap**: an overlap of the *p* orbitals of the electron-withdrawing group with the *p* orbitals of C2 and C3 of the diene (Figure 11-11). Secondary overlap helps to stabilize the transition state.

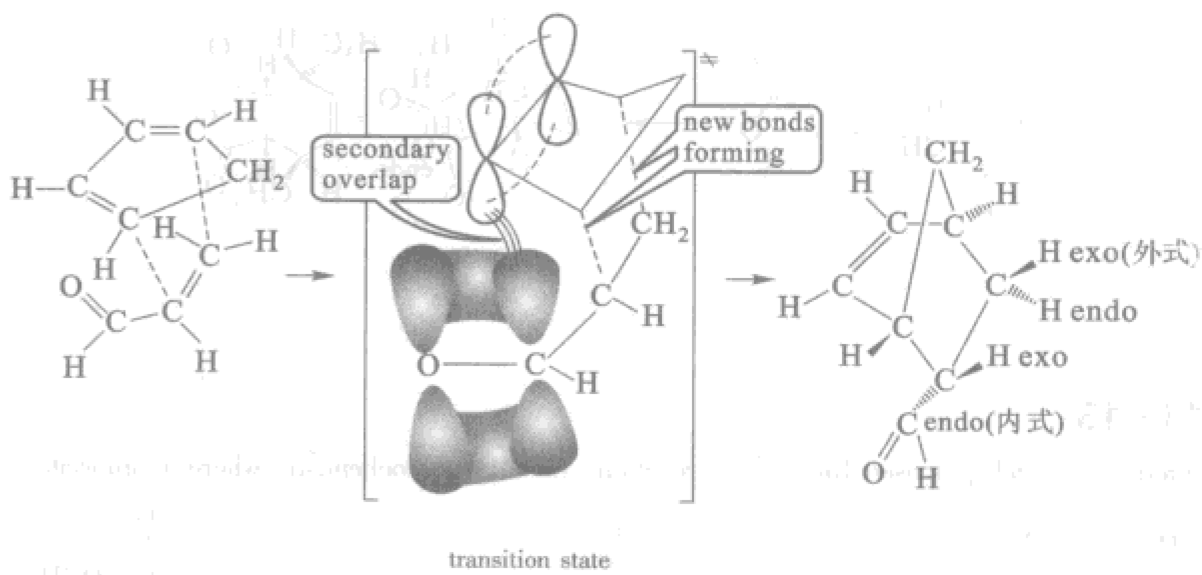
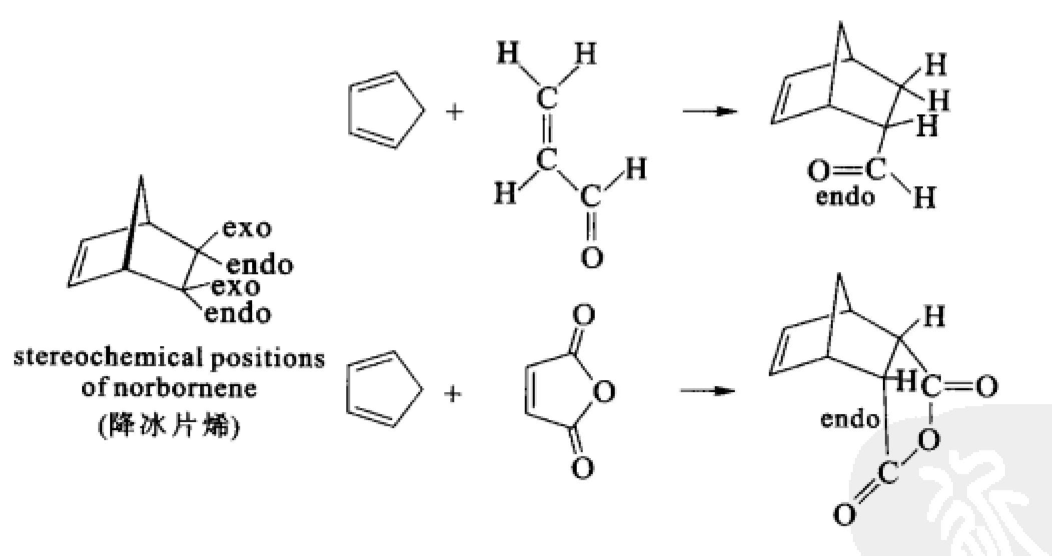
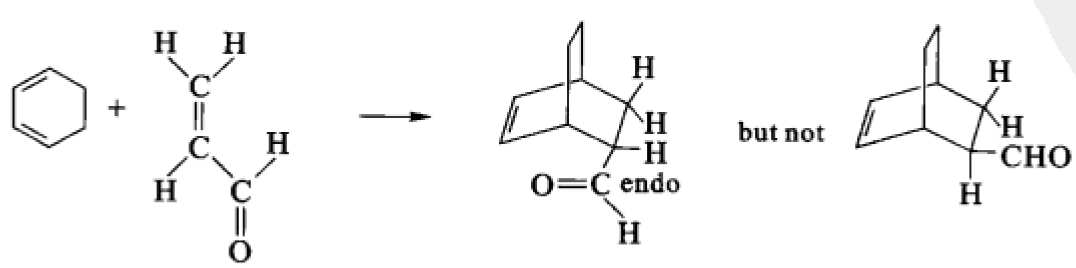


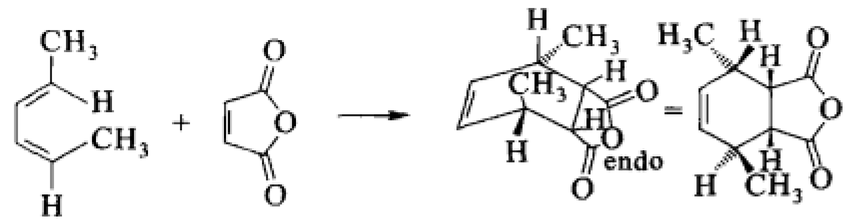
Figure 11−11 In most Diels-Alder reactions, there is *secondary overlap* between the *p* orbitals of the electron-withdrawing group and one of the central carbon atoms of the diene. Secondary overlap stabilizes the transition state, and it favors products having the electron-withdrawing groups in *endo* positions.

The influence of secondary overlap was first observed in reactions using cyclopentadiene to form bicyclic ring systems. In the bicyclic product (called *norbornene*), the electron-withdrawing substituent occupies the stereochemical position closest to the central atoms of the diene. This position is called the **endo position** because the substituent seems to be inside the pocket formed by the six-membered ring of norbornene. This stereochemical preference for the electron-withdrawing substituent to appear in the endo position is called the **endo rule.**



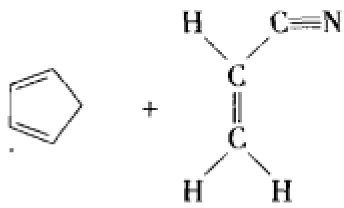
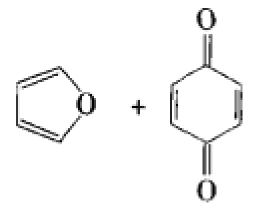
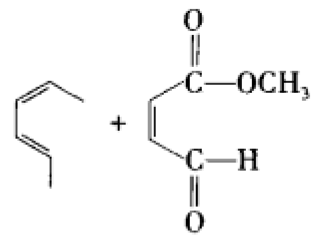
The endo rule is useful for predicting the products of many types of Diels-Alder reactions, regardless of whether they use cyclopentadiene to form norbornene systems. The following examples show the use of the endo rule with other types of Diels-Alder reactions.





PROBLEM 11-13

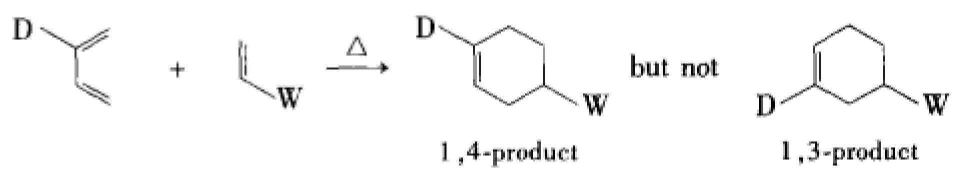
Predict the major product for each proposed Diels-Alder reaction. Include stereochemistry where appropriate.

(a)  (b)  (c) 

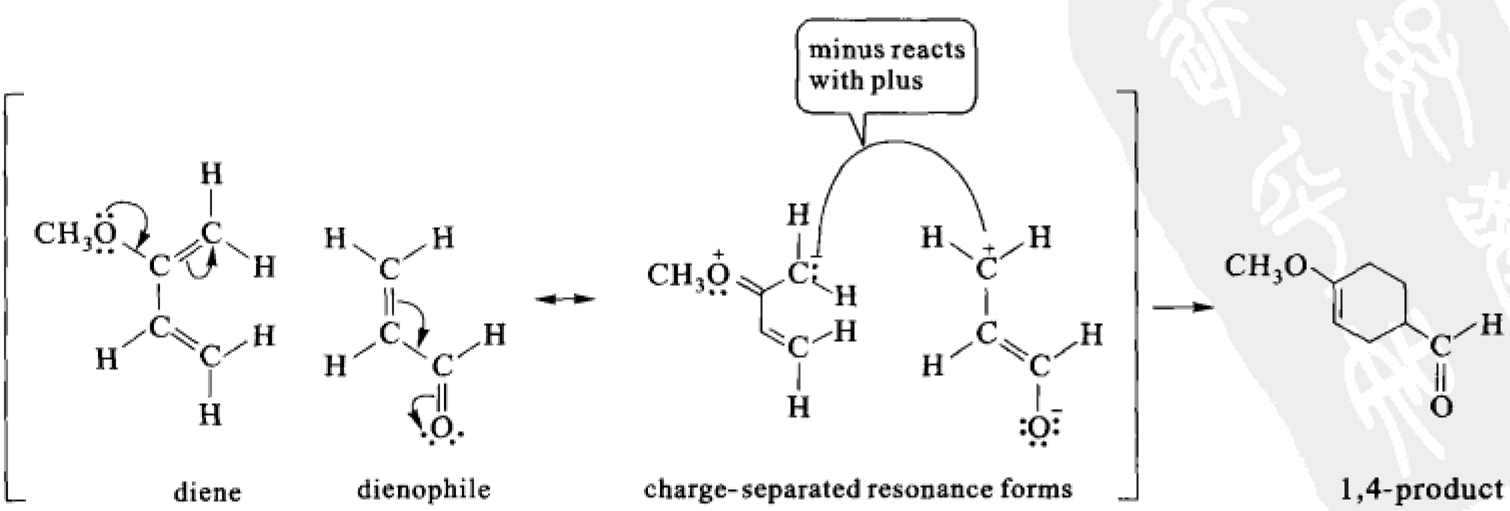
11-11B Diels-Alder Reactions Using Unsymmetrical Reagents

Even when the diene and dienophile are both unsymmetrically substituted, the Diels-Alder reaction usually gives a single product (or a major product) rather than a random mixture. We can usually predict the major product by considering how the substituents polarize the diene and the dienophile in their charge-separated resonance forms. If we then arrange the reactants to connect the most negatively charged carbon in the (electron-rich) diene with the most positively charged carbon in the (electron-poor) dienophile, we can usually predict the correct orientation. The following examples show that an electron-donating substituent (D) on the diene and an electron-withdrawing substituent (W) on the dienophile usually show either a 1,2-or 1,4-relationship in the product.

Formation of 1,4-product

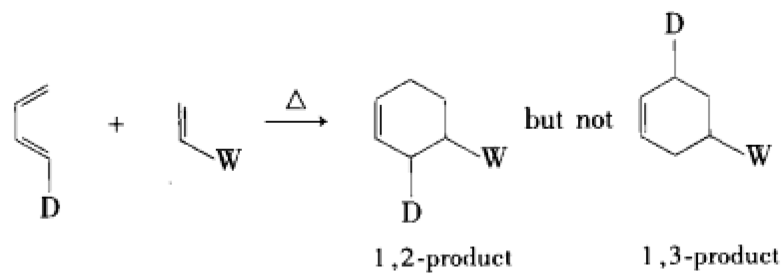


Predicting this product

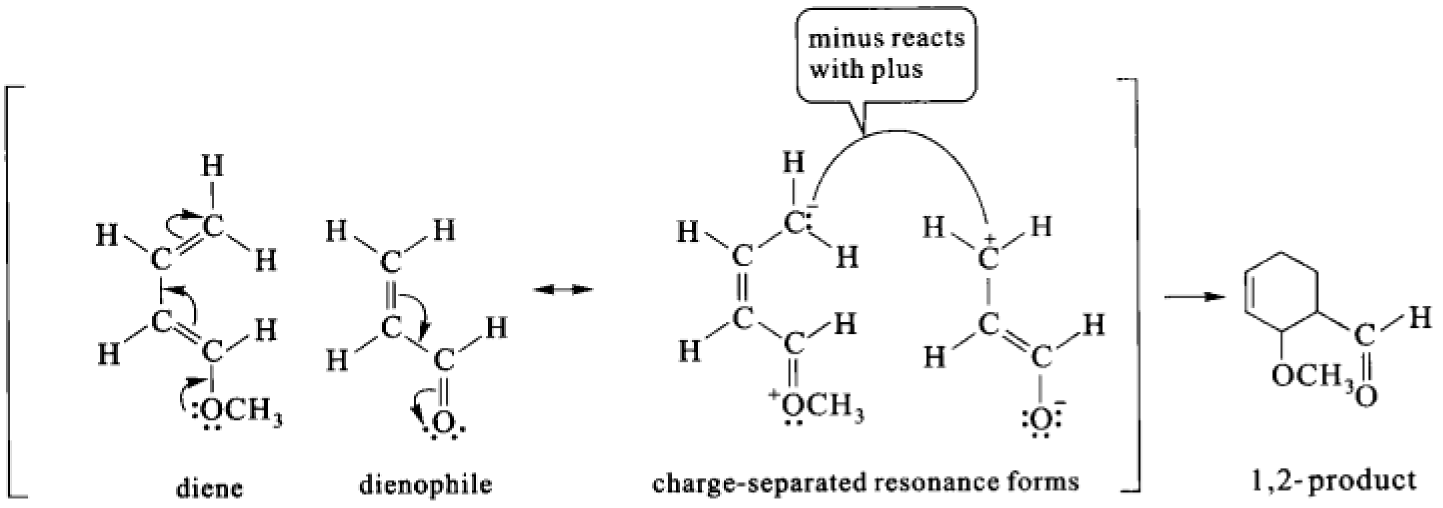


(电荷分离共振式)

Formation of 1,2-product



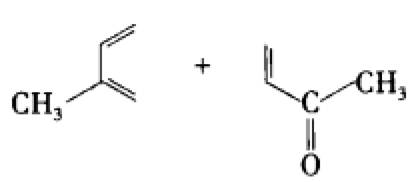
predicting this product

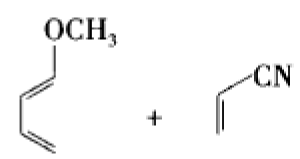


In most cases, we don't even need to draw the charge-separated resonance forms to determine which orientation of the reactants is preferred. We can predict the major products of unsymmetrical Diels-Alder reactions simply by remembering that the electron-donating groups of the diene and the electron-withdrawing groups of the dienophile usually bear either a 1,2-relationship or a 1,4-relationship in the products, but not a 1,3-relationship.

SOLVED PROBLEM 11-1

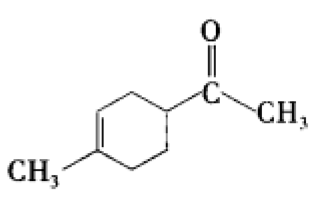
Predict the products of the following proposed Diels-Alder reactions.

(a) 

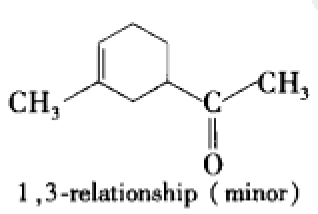
(b) 

SOLUTION

(a) The methyl group is weakly electron-donating to the diene, and the carbonyl group is electron-withdrawing from the dienophile. The two possible orientations place these groups in a 1,4-relationship or a 1,3-relationship. We select the 1,4-relationship for our predicted product. (Experimental results show a 70 : 30 preference for the 1,4-product.)

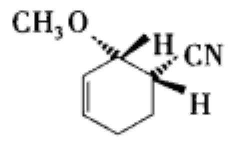


1,4-relationship (major)
(70%)

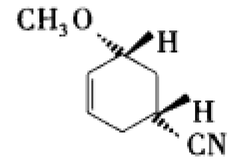


1,3-relationship (minor)
(30%)

(b) The methoxyl group ($-OCH_3$) is strongly electron-donating to the diene, and the cyano group ($-C\equiv N$) is electron-withdrawing from the dienophile. Depending on the orientation of addition, the product has either a 1,2-or a 1,3-relationship of these two groups. We select the 1,2-relationship, and the endo rule predicts cis stereochemistry of the two substituents.



1,2-relationship (product)



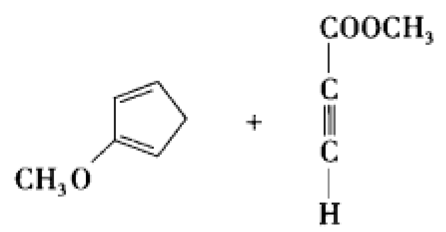
1,3-relationship (not formed)

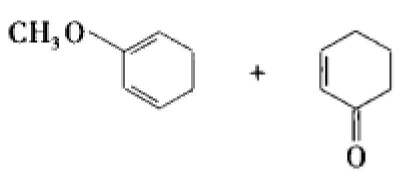
PROBLEM 11-14

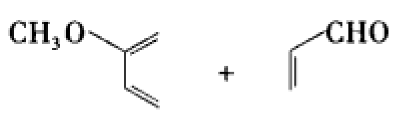
In Solved Problem 11-1, we simply predicted that the products would have a 1,2-or 1,4-relationship of the proper substituents. Draw the charge-separated resonance forms of the reactants to support these predictions.

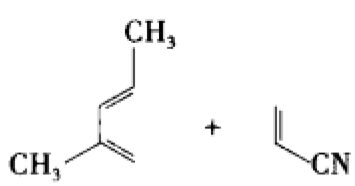
PROBLEM 11-15

Predict the products of the following Diels-Alder reactions.

(a) 

(b) 

(c) 

*(d) 

11-12 The Diels-Alder as an Example of a Pericyclic Reaction

To understand why the Diels-Alder reaction takes place, we must consider the molecular orbitals involved. The Diels-Alder is a **cycloaddition**: Two molecules combine in a one-step, **concerted reaction** to from a new ring. Cycloadditions such as the Diels-Alder are one class of **pericyclic reactions**, which involve the concerted forming and breaking of bonds within a closed ring of interacting orbitals. Figure 11-9 shows the closed loop of interacting orbitals in the Diels-Alder transition state. Each carbon atom of the new ring has one orbital involved in this closed loop.

A concerted pericyclic reaction has a single transition state, whose activation energy may be supplied by heat (thermal induction) or by ultraviolet light (photochemical induction). Some pericyclic reactions proceed only under thermal induction, and others proceed only under photochemical induction. Some pericyclic reactions take place under both thermal and photochemical conditions, but the two sets of conditions give different products.

For many years, pericyclic reactions were poorly understood and unpredictable. Around 1965, R. B. Woodward and R. Hoffmann developed a theory for predicting the results of pericyclic reactions by considering the symmetry of the molecular orbitals of the reactants and products. Their theory, called **conservation of orbital symmetry**, says that the MOs of the reactants must flow smoothly into the MOs of the products without any dras-

tic changes in symmetry. In that case, there will be bonding interactions to help stabilize the transition state. Without these bonding interactions in the transition state, the concerted cyclic reaction cannot occur. Conservation of symmetry has been used to develop "rules" to predict which pericyclic reactions are feasible and what products will result. These rules are often called the "**Woodward-Hoffmann rules.**"

11−12A Conservation of Orbital Symmetry in the Diels-Alder Reaction

We will not develop all the Woodward-Hoffmann rules, but we will show how the molecular orbitals can indicate whether a cycloaddition will take place. The simple Diels-Alder reaction of butadiene with ethylene serves as our first example. The molecular orbitals of butadiene and ethylene are represented in Figure 11−12. Butadiene, with four atomic *p* orbitals, has four molecular orbitals: two bonding MOs (filled) and two antibonding MOs (vacant). Ethylene, with two atomic *p* orbitals, has two MOs: a bonding MO (filled) and an antibonding MO (vacant).

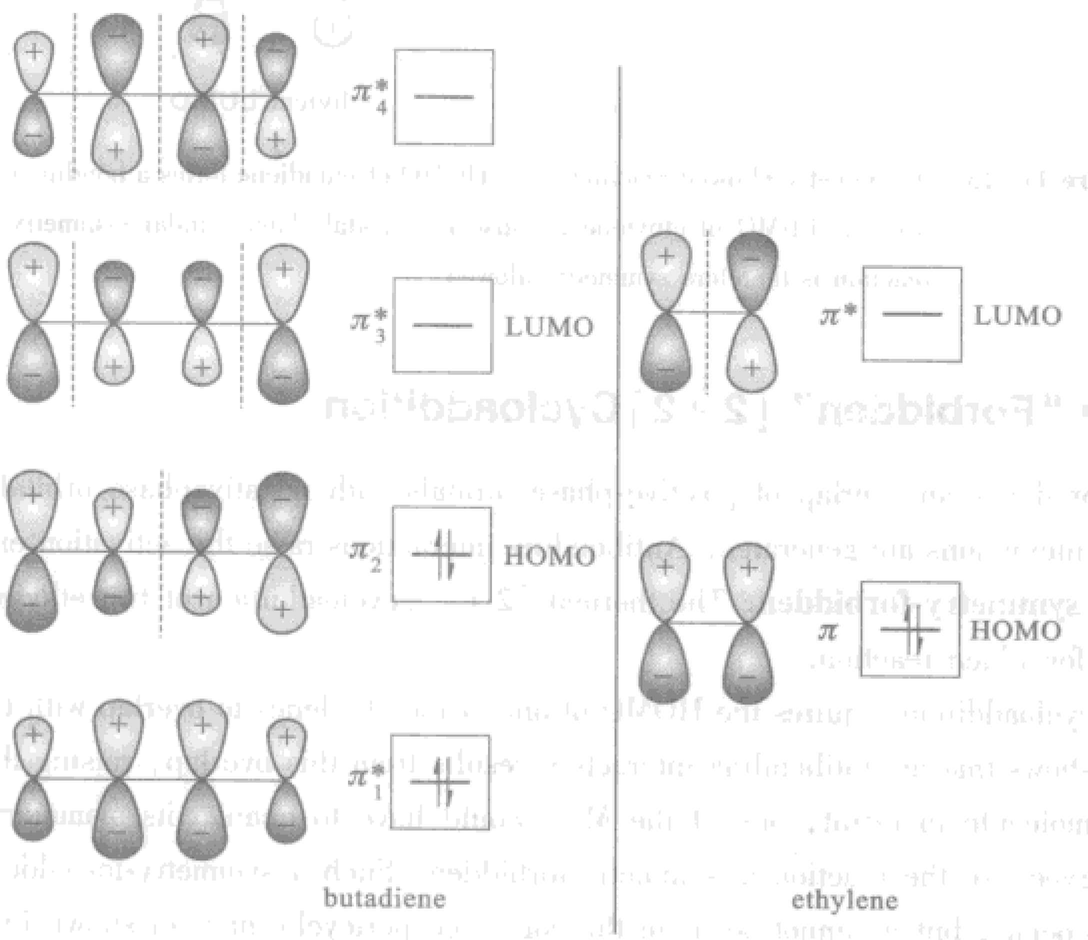


Figure 11−12 Molecular orbitals of butadiene and ethylene.

In the Diels-Alder reaction, the diene acts as the electron-rich nucleophile, and the dienophile acts as the electron-poor electrophile. If we imagine the diene contributing a pair of electrons to the dienophile, the highest-energy electrons of the diene require the least activation energy for such a donation. The electrons in the highest-energy occupied orbital, called the **Highest Occupied Molecular Orbital** (**HOMO**), are the important ones because they are the most weakly held. The HOMO of butadiene is π_2, and its symmetry determines the course of the reaction.

The orbital in ethylene that receives these electrons is the lowest-energy orbital available, the **Lowest Unoccupied Molecular Orbital** (**LUMO**). In ethylene, the LUMO is the π^* antibonding orbital. If the electrons in the HOMO of butadiene can flow smoothly into the LUMO of ethylene, a concerted reaction can take place.

Figure 11−13 shows that the HOMO of butadiene has the correct symmetry to overlap in phase with the LU-

MO of ethylene. Having the correct symmetry means the orbitals that form the new bonds can overlap constructively: plus with plus and minus with minus. These bonding interactions stabilize the transition state and promote the concerted reaction. This favorable result shows the reaction is **symmetry-allowed.** The Diels-Alder reaction is common, and this theory correctly predicts a favorable transition state.

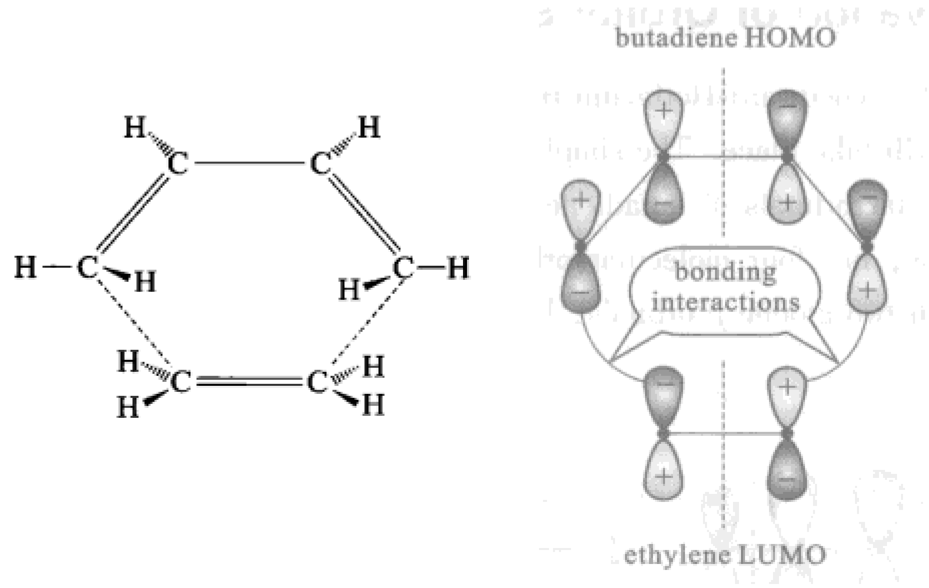


Figure 11−13 A symmetry-allowed reaction. The HOMO of butadiene forms a bonding overlap with the LUMO of ethylene because the orbitals have similar symmetry. This reaction is therefore symmetry-allowed.

11−12B The "Forbidden" [2 +2] Cycloaddition

If a cycloaddition produces an overlap of positive-phase orbitals with negativephase orbitals (destructive overlap), antibonding interactions are generated. Antibonding interactions raise the activation energy; thus the reaction is classified as **symmetry-forbidden.** The thermal [2 +2] cycloaddition of two ethylenes to give cyclobutane is a symmetry-forbidden reaction.

This [2 +2] cycloaddition requires the HOMO of one of the ethylenes to overlap with the LUMO of the other. Figure 11−14 shows that an antibonding interaction results from this overlap, raising the activation energy. For a cyclobutane molecule to result, one of the MOs would have to change its symmetry. Orbital symmetry would not be conserved, so the reaction is symmetry-forbidden. Such a symmetry-forbidden reaction can occasionally be made to occur, but it cannot occur in the concerted pericyclic manner shown in the figure.

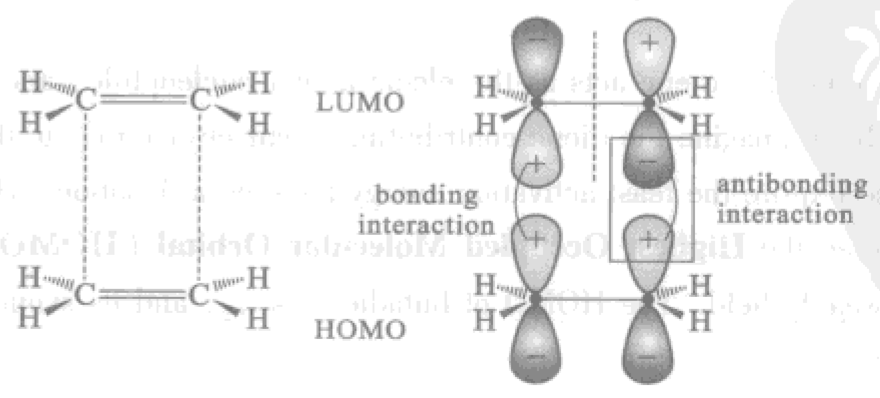
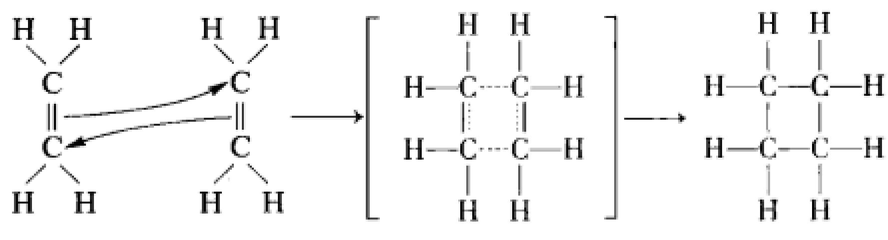


Figure 11−14 A symmetry-forbidden reaction. The HOMO and LUMO of two ethylene molecules have different symmetries, and they overlap to form an antibonding interaction. The concerted [2 +2] cycloaddition is therefore symmetry-forbidden.



11-12C Photochemical Induction of Cycloadditions

When ultraviolet light rather than heat is used to induce pericyclic reactions, our predictions are generally reversed. For example, the [2 + 2] cycloaddition of two ethylenes is photochemically "allowed." When a photon with the correct energy strikes ethylene, one of the pi electrons is excited to the next higher molecular orbital (Figure 11-15). This higher orbital, formerly the LUMO, is now occupied: It is the new HOMO*, the HOMO of the excited molecule.

The HOMO* of the excited ethylene molecule has the same symmetry as the LUMO of a ground-state ethylene. An excited molecule can react with a ground-state molecule to give cyclobutane (Figure 11-16). The [2 + 2] cycloaddition is therefore *photochemically allowed* but *thermally forbidden*. In most cases, photochemically allowed reactions are thermally forbidden, and thermally allowed reactions are photochemically forbidden.

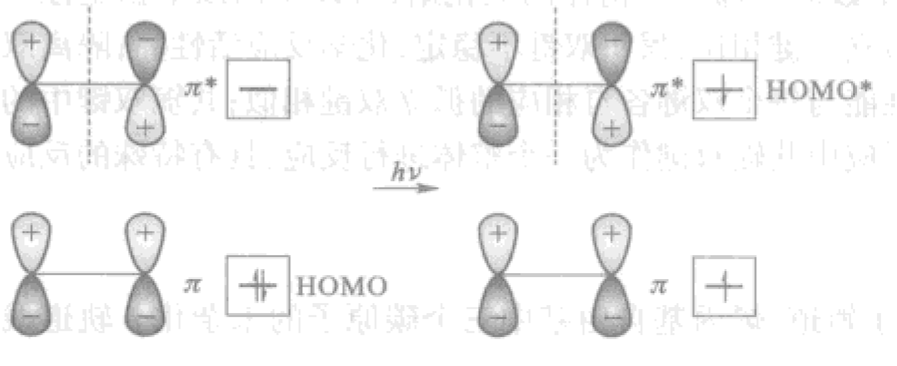


Figure 11-15 The effect of ultraviolet light on ethylene. Ultraviolet light excites one of the ethylene pi electrons into the antibonding orbital. The antibonding orbital is now occupied, so it is the new HOMO*.

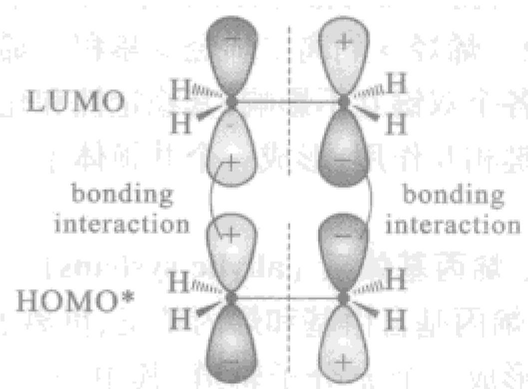


Figure 11-16 Photochemical [2 + 2] cycloaddition. The HOMO* of the excited ethylene overlaps favorably with the LUMO of an unexcited (ground-state) molecule. This reaction is symmetry-allowed.

PROBLEM 11-16

Show that the [4 + 2] Diels-Alder reaction is photochemically forbidden.

PROBLEM 11-17

(a) Show that the [4 + 4] cycloaddition of two butadiene molecules to give cycloocta-1, 5-diene is thermally forbidden but photochemically allowed.

(b) There is a different, thermally allowed cycloaddition of two butadiene molecules. Show this reaction, and explain why it is thermally allowed. (*Hint*: Consider the dimerization of cyclopentadiene.)

Summary in Chinese

本章概要

一、共轭烯烃（conjugated alkenes）

1. 共轭烯烃：根据双键在二烯烃或多烯烃分子中的位置可以分为共轭双键（双键被一个单键隔开）、隔离双键（双键被两个或两个以上单键隔开）和累积双键（两个连续的双键）。含共轭双键的烯烃称为共轭烯烃。

2. 共轭体系的 π 键分子轨道：以 1，3－丁二烯为例，四个碳原子彼此平行的未杂化 p 轨道重叠形成四个 π 键分子轨道。其中两个为成键轨道（π_1，π_2），两个为反键轨道（π_3^*，π_4^*）。四个 p 电子占据 π_1 和 π_2 成键轨道，π_3^* 和 π_4^* 反键轨道中无电子填充。每个成键分子轨道中的两个 π 电子的运动范围与孤立双键中的 π 电子不同，并不只局限于两个原子间运动，而是扩展到共轭双键的四个碳原子之间。这种电子离域现象可以使分子的能量降低，从而提高分子的稳定性。

3. 共轭烯烃的结构特征：共轭烯烃中两个双键之间的单键的键长比一般的 σ 键略短一些。这种特殊的 σ 键在室温下可以旋转，如 1，3－丁二烯有两种构象异构体，单键－反式和单键－顺式，反式异构体比顺式的稳定。

4. 共轭烯烃的稳定性：通过比较相同碳氢原子数的二烯烃异构体的氢化焓，可以得出以下稳定性顺序：共轭二烯烃 > 隔离二烯烃 > 累积二烯烃。与孤立双键相比，累积双键不稳定，化学反应活性高；隔离双键中的各个双键互不影响，其稳定性和化学反应性能与每个双键各自相应的孤立双键相似；共轭双键中的各个双键相互作用，形成一个共轭体系。在化学反应中共轭双键作为一个整体进行反应，具有特殊的反应规律。

二、烯丙基体系（allylic systems）

1. 烯丙基自由基和烯丙基正、负离子的 π 分子轨道：烯丙基自由基中三个碳原子的未杂化 p 轨道线性组合形成三个 π 分子轨道，其中一个为成键轨道（π_1），一个为非成键轨道（π_2），还有一个反键轨道（π_3^*）。烯丙基正、负离子的 π 分子轨道的形成与烯丙基自由基相同，三者之间只是在 π 电子数目上不同。烯丙基自由基和正、负离子的成键轨道上都有两个自旋相反的 π 电子，所不同的是非键轨道上的电子数，烯丙基自由基的非键轨道上有一个 p 电子，正离子的非键轨道上没有电子，而负离子的非键轨道上有两个电子。π 电子在三个碳原子之间运动，因此，在这些烯丙基中间体中 C1—C2 和 C2—C3 各具有 1/2 个 π 键。对于烯丙基自由基而言，C1 和 C3 上各拥有 1/2 个未成对电子；在烯丙基碳正离子和碳负离子中，正、负电荷平均分布在 C1 和 C3 原子上。由于烯丙基中间体中这种电子离域现象，使电荷分散，中间体能量降低，稳定性提高。

2. 烯丙基中间体的稳定性和烯丙位原子或基团的化学性质：对于不对称取代的烯丙基自由基和碳正离子，自由基或正电荷分布在烷基取代基较多的碳原子上时更稳定。烯丙基自由基的稳定性大于叔碳自由基，烯丙基碳正离子的稳定性小于叔碳正离子，但稍大于仲碳正离子。由于烯丙基自由基能量低、易生成，烯丙位氢原子易发生自由基取代反应；烯丙位卤素原子或磺酸根易发生亲核取代反应。

三、烯丙位自由基溴代反应（free-radical allylic bromination）

$$\mathrm{RCH{=}CH{-}CH_2R'} \xrightarrow[h\nu]{\mathrm{NBS}} \mathrm{RCH{=}CH{-}\underset{\displaystyle\overset{|}{}}{\overset{\mathrm{Br}}{\overset{|}{C}}}HR'} + \mathrm{R\overset{\mathrm{Br}}{\overset{|}{C}}H{-}CH{=}CHR'}$$

☆ 溴化剂 N－溴代丁二酰亚胺（NBS）可与反应中生成的少量 HBr 反应产生低浓度溴，使丙烯或其衍生物发生烯丙位氢原子溴代反应。如加入的溴浓度过大，易发生双键加成副反应。

☆ 经过烯丙基型自由基中间体的反应，都会发生烯丙基位置异构化。如果烯丙基中两个带部分未成对电子的碳原子（C1 和 C3）上的取代基相同，得到同一种溴化产物，但如果取代基不相同，则生成两种溴化产物。

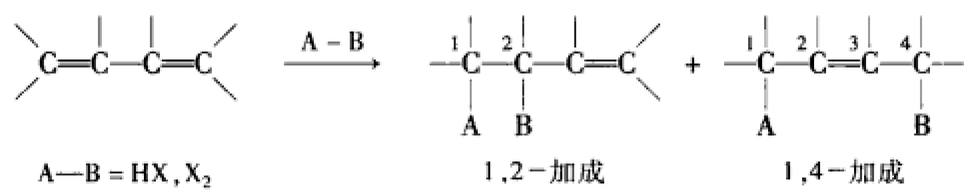
四、烯丙基卤代物的亲核取代反应（nucleophilic substitution of allylic halides）

1. S_N1 亲核取代反应：普通伯卤代烷不能发生 S_N1 取代反应，但烯丙基碳卤键容易发生异裂，经过稳定的烯丙基碳正离子发生 S_N1 取代反应。经过烯丙基碳正离子中间体的反应，像烯丙基自由基反应一样都会发生烯丙基位置异构化，但不发生 1,2－氢转移和 1,2－烷基转移的普通碳正离子重排反应。如果烯丙基碳正离子中，两个带部分正电荷的碳原子上的取代基不相同，则生成两种取代产物，其中亲核试剂连接到烷基取代基较多的碳原子上的产物为主产物。

2. S_N2 亲核取代反应：当亲核试剂进攻与离去基团相连的烯丙位碳原子时，烯丙基中 π 键的 p 轨道与被进攻碳原子的 p 轨道平行，三个 p 轨道上的 π 电子发生离域，使过渡态能量降低。因此，烯丙基卤代物和磺酸烯丙酯类化合物的 S_N2 取代反应活性大大提高，反应速率明显加快。

五、共轭二烯烃的 1,2－和 1,4－加成反应（1,2-and 1,4-addition of conjugated dienes）

1. 1,2－和 1,4－加成反应：

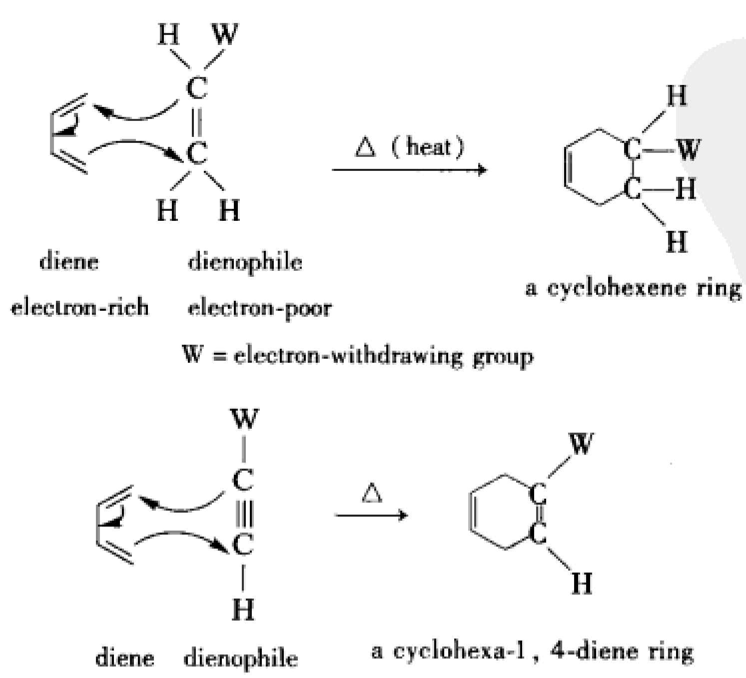


☆ 共轭二烯能与卤素、卤化氢等发生亲电加成反应，生成两种产物。亲电试剂加在共轭二烯的两个相邻碳原子上生成 1,2－加成产物，或称简单加成产物；或者加到共轭二烯两端的碳原子上，生成 1,4－加成产物，或称共轭加成产物。两种产物的比例取决于产物稳定性和反应条件。

2. 共轭二烯加成反应的动力学和热力学控制：1,2－加成反应过渡态的能量低于 1,4－加成反应过渡态的能量，因此，1,2－加成反应为动力学有利的反应，降低反应温度可提高 1,2－加成反应产物的比例。1,4－加成产物的能量低于 1,2－加成产物的能量，共轭加成产物为内烯烃，稳定性比端烯烃好。因此，1,4－加成反应为热力学有利的反应，适当升高反应温度可提高 1,4－加成产物的比例。升温时，1,2－加成产物可异构化生成 1,4－加成产物。

六、第尔斯－阿尔德反应（Diels-Alder reaction）

1. 第尔斯－阿尔德反应：



☆ 共轭二烯（diene）与亲双烯体（dienophile），即烯烃或炔烃，在加热条件下可发生［4＋2］环加成反

应。这种反应又称为双烯合成反应，是合成六元环化合物的一个重要方法。共轭二烯 2、3 位碳原子上带给电子基团或亲双烯体中带吸电子基团有利于环化反应在较温和的条件下进行。

2. 第尔斯－阿尔德反应的立体化学：共轭二烯必须首先通过单键旋转从单键－反式（*s*-trans）构象转变为单键－顺式（*s*-cis）构象，才能与亲双烯体发生[4＋2]环化反应，如果因为某种原因单键－反式构象不能转变为单键－顺式构象，则反应不能发生。单键－顺式构象稳定有利于反应。反应经过协同机理，对共轭二烯和亲双烯体来说均为顺式加成反应（syn addition）。

3. 内式规则（endo rule）：当环状共轭二烯与带羰基或氰基的烯烃反应时，烯烃上羰基和氰基的 *p* 轨道尽可能接近共轭二烯 C2 和 C3 原子上的 *p* 轨道，形成二级重叠，使反应过渡态能量降低，由此导致反应总是生成羰基或氰基处于内式的双环产物。反应的这种立体化学选择性称为内式规则。

4. 第尔斯－阿尔德反应的区域选择性：不对称的双烯和亲双烯体反应时，双烯中最富电子的碳原子总是与亲双烯体中最缺电子的碳原子成键。由此可以判断反应产物的区域选择性。具体来说，2 位带给电子基团的双烯与带吸电子基团的烯烃反应总是生成 1,4－二取代环己烯，而 1 位带给电子基团的双烯与带吸电子基团的烯烃反应则生成 1,2－二取代环己烯。

七、周环反应（pericyclic reaction）

1. 轨道对称守恒原理（conservation of orbital symmetry, Woodward-Hoffmann rule）：反应成键过程是分子轨道的重新组合过程，反应过程中分子轨道的对称性必须是守恒的，即反应物和产物的分子轨道的对称性必须一致，才容易进行反应，称为对称性允许；反之，轨道对称性不一致，反应就难以进行，称为对称性禁阻。

2. 周环反应：周环反应一般在加热或光照条件下进行，反应经过双分子协同反应机理，遵守轨道对称守恒原理。双烯填充电子的能量最高占据分子轨道（highest occupied molecular orbital，简称 HOMO）与亲双烯体未填充电子的能量最低未占分子轨道（lowest unoccupied molecular orbital，简称 LUMO）之间的[4＋2]环加成反应，即第尔斯－阿尔德反应为轨道对称性允许的反应；一个烯烃分子的 HOMO 与另一个烯烃分子的 LUMO 之间的[2＋2]环加成反应是轨道对称性禁阻的反应，但在紫外线照射下，电子被激发跃迁后，激发态烯烃的 HOMO* 与基态烯烃的 LUMO 之间的[2＋2]环加成反应是光化学允许的反应。

Essential Problem-Solving Skills in Chapter 11

1. Show how to construct the molecular orbitals of ethylene, butadiene, and the allylic system. Show the electronic configurations of ethylene, butadiene, and the allyl cation, radical, and anion.
2. Recognize reactions that are enhanced by resonance stabilization of the intermediates, such as free-radical reactions and cationic reactions. Develop mechanisms to explain the enhanced rates and observed products, and draw resonance forms of the stabilized intermediates.
3. Predict the products of Diels-Alder reactions, including the orientation of cycloaddition with unsymmetrical reagents and the stereochemistry of the products.
4. Predict which cycloadditions will be thermally allowed and which will be photochemically allowed by comparing the molecular orbitals of the reactants.

Study Problems

11－18 Briefly define each term and give an example.

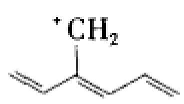
(a) an allylic alcohol（烯丙基醇）
(b) an endo product（内式产物）
(c) conjugated double bonds（共轭双键）
(d) cumulated double bonds（累积双键）
(e) isolated double bonds（隔离双键）
(f) a molecular orbital（分子轨道）
(g) a nonbonding MO（非键分子轨道）
(h) an antibonding MO（反键分子轨道）

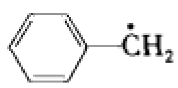
(i) an allylic radical（烯丙基自由基）
(j) an *s*-cis conformation（单键顺式构象）
(k) a 1,2-addition
(l) a 1,4-addition
(m) a cycloaddition（环加成）
(n) kinetic control（动力学控制）
(o) a Diels-Alder reaction
(p) thermodynamic control（热力学控制）
(q) a dienophile（亲双烯体）
(r) a concerted reaction（协同反应）
(s) a HOMO, a HOMO*, and a LUMO
(t) a symmetry-forbidden reaction（对称禁阻反应）
(u) a substituted allene（取代丙二烯）

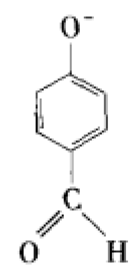
11−19 Predict the products of the following reactions.

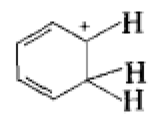
(a) allyl bromide + cyclohexyl magnesium bromide
(b) cyclopentadiene + anhydrous HCl
(c) 2-methylpropene + NBS, light
(d) 1-pentene + NBS, light
(e) 1,3-butadiene + bromine water
(f) 1,3,5-hexatriene + bromine in CCl_4
(g) 1-(bromomethyl)-2-methylcyclopentene, heated in methanol
(h) cyclopentadiene + methyl acrylate, $CH_2{=}CH{-}COOCH_3$
(i) 1,3-cyclohexadiene + $CH_3OOC{-}C{\equiv}C{-}COOCH_3$
(j) furan + *trans*-1,2-dicyanoethylene

11−20 Draw the important resonance contributors for the following cations, anions, and radicals.

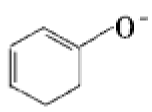
(a) 

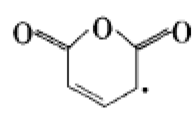
(b) 

(c) 

(d) 

(e)

(f) 

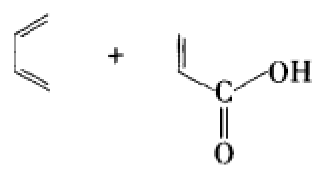
(g) 

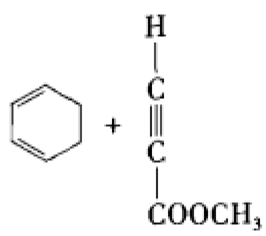
11−21 When *N*-bromosuccinimide is added to 1-hexene and a sunlamp is shone on the mixture, three products result.

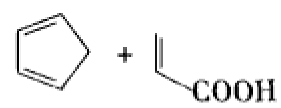
(a) Give the structures of these three products.

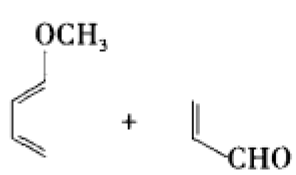
(b) Propose a mechanism that accounts for the formation of these three products.

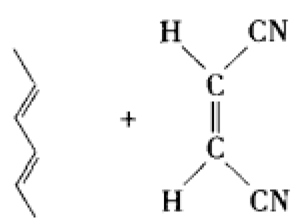
11−22 Predict the products of the following Diels-Alder reactions. Include stereochemistry where appropriate.

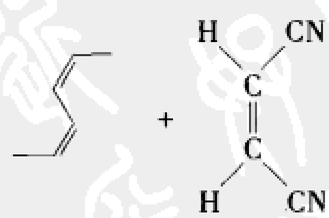
(a) 

(b) 

(c) 

(d) 

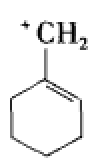
(e) 

(f) 

11−23 For each structure,

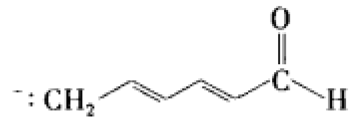
1. Draw all the important resonance contributors.
2. Evaluate the significance of each resonance contributor.

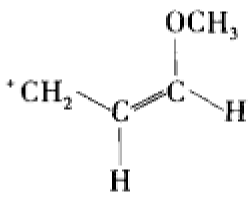
(a)

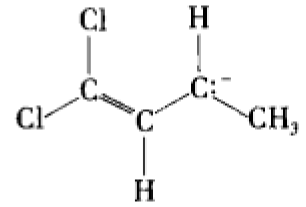
(b) 

(c) $^{-}:CH_2{-}\overset{\overset{O}{\|}}{C}{-}CH_3$

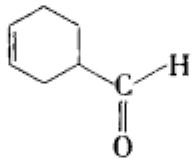
(d) $CH_3{-}\overset{\overset{O^-}{|}}{C}{=}\overset{+}{N}H_2$

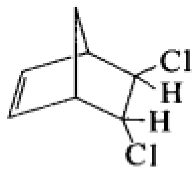
(e) 

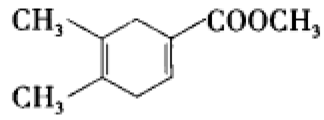
(f) 

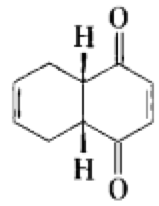
(g) 

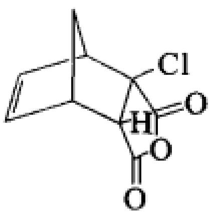
11−24 Show how Diels-Alder reactions might be used to synthesize the following compounds.

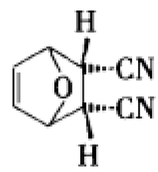
(a) 

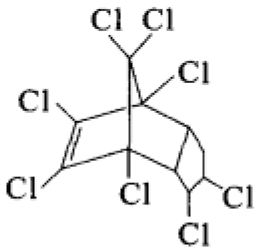
(b) 

(c) 

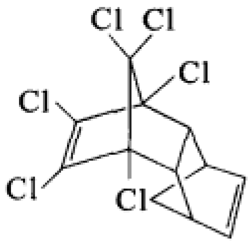
(d) 

(e) 

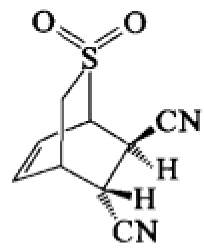
(f) 

(g) 

chlordane（氯丹，八氯代甲桥茚）

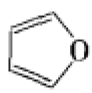
(h) 

aldrin（艾氏剂，氯甲桥萘）

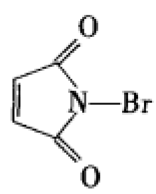
(i) 

11−25 Furan and maleimide undergo a Diels-Alder reaction at 25 ℃ to give the endo isomer of the product. When the reaction takes place at 90 ℃, however, the major product is the exo isomer. Further study shows that the endo isomer of the product isomerizes to the exo isomer at 90 ℃.

furan:
（呋喃）



maleimide:
（马来酰亚胺）



(**a**) Draw and label the endo and exo isomers of the Diels-Alder adduct of furan and maleimide.

(**b**) Which isomer of the product would you usually expect from this reaction? Explain why this isomer is usually favored.

(**c**) Examine your answer to (b) and determine whether this answer applies to a reaction that is kinetically controlled or one that is thermodynamically controlled, or both.

(**d**) Explain why the endo isomer predominates when the reaction takes place at 25 ℃ and why the exo isomer predominates at 90 ℃.

Chapter 12
Infrared and Ultraviolet Spectroscopy

12-1 Introduction

One of the most important tasks of organic chemistry is the determination of organic structures. When an interesting compound is isolated from a natural source, its structure must be completely determined before a synthesis is begun. Whenever we run a reaction, we must determine whether the product has the desired structure. The structure of an unwanted product must be known so the reaction conditions can be altered to favor the desired product.

In many cases, a compound can be identified by chemical means. We find the molecular formula by analyzing the elemental composition and determining the molecular weight. If the compound has been characterized before, we can compare its physical properties (melting point, boiling point, etc.) with the published values. Chemical tests can suggest the functional groups and narrow the range of possible structures before the physical properties are used to make an identification.

These procedures are not sufficient, however, for complex compounds that have never been synthesized and characterized. They are also impractical with compounds that are difficult to obtain, because a relatively large sample is required to complete the elemental analysis and all the functional group tests. We need analytical techniques that work with tiny samples and that do not destroy the sample.

Spectroscopic techniques often meet these requirements. **Absorption spectroscopy** is the measurement of the amount of light absorbed by a compound as a function of the wavelength of light. In general, a sample is irradiated by a light source, and the amount of light transmitted at various wavelengths is measured by a detector and plotted on a graph. Unlike chemical tests, most spectroscopic techniques are *nondestructive*; that is, the sample is not destroyed. Many different kinds of spectra can be measured with little or no loss of sample.

In this book, we cover four spectroscopic or related techniques that serve as powerful tools for structure determination in organic chemistry:

Infrared (IR) spectroscopy, covered in this chapter, observes the vibrations of bonds and provides evidence of the functional groups present.

Ultraviolet (UV) spectroscopy, also covered in this Chapter, observes electronic transitions and provides information on the electronic bonding in the sample.

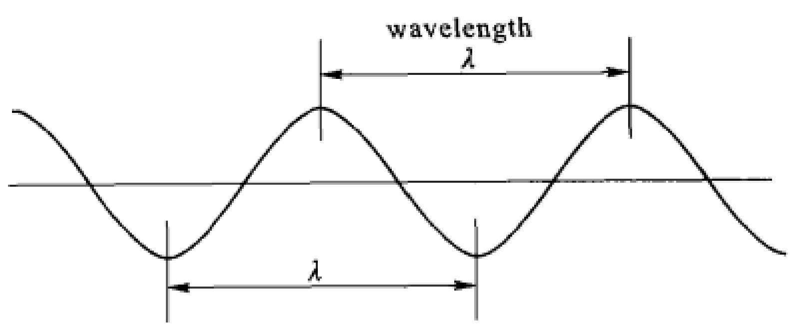
Nuclear magnetic resonance (NMR) spectroscopy, covered in Chapter 13, observes the chemical environments of the hydrogen atoms (or the carbon atoms) and provides evidence for the structure of the alkyl groups and clues to the functional groups.

Mass spectrometry (MS), also covered in Chapter 13, bombards molecules with electrons and breaks them apart. Analysis of the masses of the fragments gives the molecular weight, possibly the molecular formula, and clues to the structure and functional groups. Less than a milligram of sample is destroyed in this analysis.

These spectroscopic techniques are complementary, and they are most powerful when used together. In many cases, an unknown compound cannot be completely identified from one spectrum without additional information, yet the structure can be determined with confidence using two or more different types of spectra.

12-2 The Electromagnetic Spectrum

Visible light, infrared light, ultraviolet light, microwaves, and radio waves are examples of electromagnetic radiation. They all travel at the speed of light, about 3×10^{10} cm/s but they differ in frequency and wavelength. The **frequency** of a wave is the number of complete wave cycles that pass a fixed point in a second. Frequency, represented by the Greek letter ν (nu), is usually given in hertz (HZ), meaning cycles per second. The **wavelength**, represented by the Greek letter λ (lambda), is the distance between any two peaks (or any two troughs) of the wave.



The wavelength and frequency, which are inversely proportional, are related by the equation

$$\nu\lambda = c \text{ or } \lambda = \frac{c}{\nu}$$

where

c = speed of light (3×10^{10} cm/s)

ν = frequency in hertz

λ = wavelength in centimeters

Electromagnetic waves travel as **photons**, which are massless packets of energy. The energy of a photon is proportional to its frequency and inversely proportional to its wavelength. A photon of frequency ν (or wavelength λ) has an energy given by

$$E = h\nu = \frac{hc}{\lambda}$$

where h is Planck's constant, 6.62×10^{-37} kJ·s. Under certain conditions, a molecule struck by a photon may absorb the photon's energy. In this case, the molecule's energy is increased by an amount equal to the photon's energy, $h\nu$. For this reason, we often represent the irradiation of a reaction mixture by the symbol $h\nu$.

The **electromagnetic spectrum** is the range of all possible frequencies, from zero to infinity. In practice, the spectrum ranges from the very low radio frequencies used to communicate with submarines to the very high frequencies of gamma rays. Figure 12-1 shows the wavelength and energy relationships of the various parts of the electromagnetic spectrum.

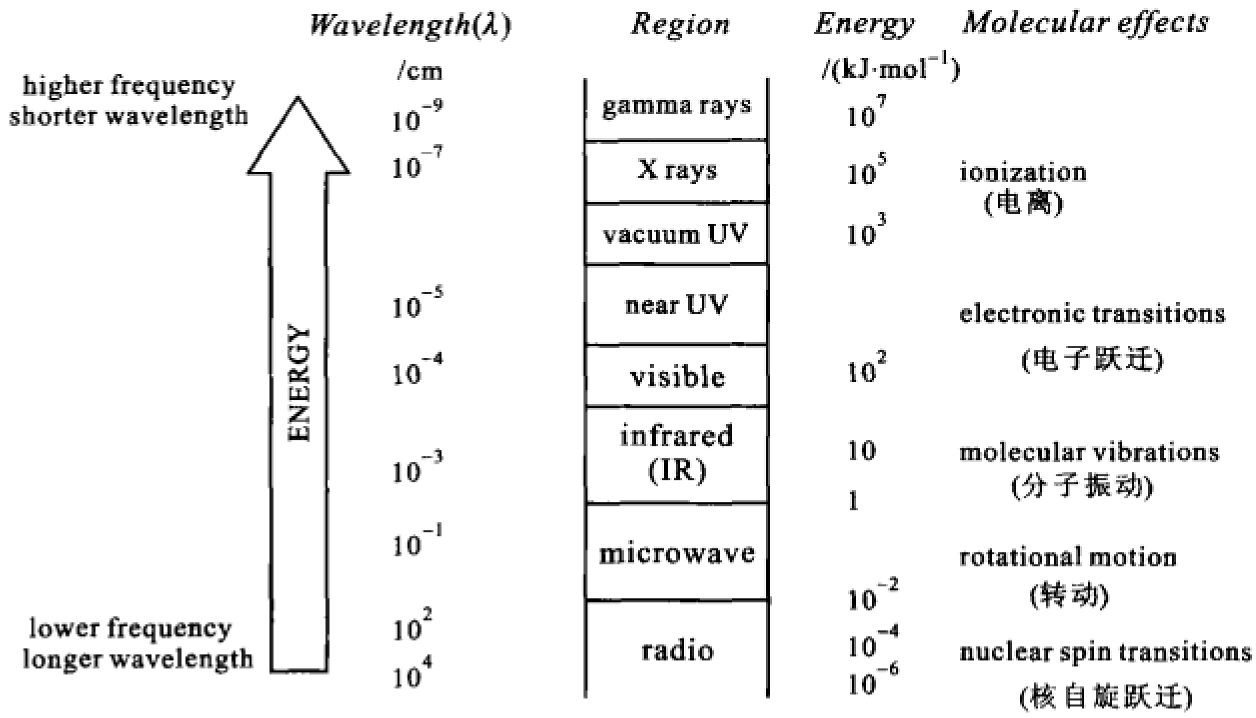


Figure 12−1 The electromagnetic spectrum.

The electromagnetic spectrum is continuous, and the exact positions of the dividing lines between the different regions are somewhat arbitrary. Toward the top of the spectrum in Figure 12−1 are the higher frequencies, shorter wavelengths, and higher energies. Toward the bottom are the lower frequencies, longer wavelengths, and lower energies. X rays (very high energy) are so energetic that they excite electrons past all the energy levels, causing ionization. Energies in the ultraviolet-visible range excite electrons to higher energy levels within molecules. Infrared energies excite molecular vibrations, and microwave energies excite rotations. Radio-wave frequencies (very low energy) excite the nuclear spin transitions observed in NMR spectroscopy.

12−3 The Infrared Region

The infrared (from the Latin, *infra*, meaning "below" red) region of the spectrum corresponds to frequencies from just below the visible frequencies to just above the highest microwave and radar frequencies: wavelengths of about 8×10^{-5} cm to 1×10^{-2} cm. Common infrared spectrometers operate in the middle of this region, at wavelengths between 2.5×10^{-4} cm and 25×10^{-4} cm, corresponding to energies of about 4.6 to 46 kJ/mol. Infrared photons do not have enough energy to cause electronic transitions, but they can cause groups of atoms to vibrate with respect to the bonds that connect them. Like electronic transitions, these vibrational transitions correspond to distinct energies, and molecules absorb infrared radiation only at certain wavelengths and frequencies.

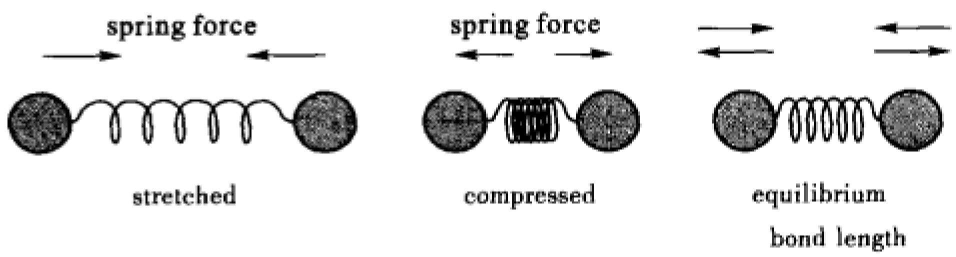
The position of an infrared band is specified by its wavelength (λ), measured in *microns* (μm). A micron (or *micrometer*) corresponds to one millionth (10^{-6}) of a meter, or 10^{-4} cm. A more common unit, however, is the **wavenumber** (σ), which corresponds to the number of cycles (wavelengths) of the wave in a centimeter. The wavenumber is the reciprocal of the wavelength (in centimeters). Since 1 cm = 10 000 μm, the wavenumber can be calculated by dividing 10 000 by the wavelength in microns. The units of the wavenumber are cm^{-1} (*reciprocal centimeters*).

$$\sigma\ (\text{cm}^{-1}) = \frac{1}{\lambda\ (\text{cm})} = \frac{10\,000\ \mu\text{m/cm}}{\lambda\ (\mu\text{m})}$$

The wavenumber is proportional to the frequency (ν) of the wave, so it is also proportional to the energy of a photon of this frequency ($E = h\nu$).

12−4 Molecular Vibrations

Before discussing characteristic infrared absorptions, it's helpful to understand some theory about the vibrational energies of molecules. The following drawing shows how a covalent bond between two atoms acts like a spring. If the bond is stretched, a restoring force pulls the two atoms together toward their equilibrium bond length. If the bond is compressed, the restoring force pushes the two atoms apart. If the bond is stretched or compressed and then released, the atoms vibrate.



The frequency of the stretching vibration depends on the masses of the atoms and the stiffness of the bond. Heavier atoms vibrate more slowly than lighter ones; for example, the characteristic frequency of a C—D bond is lower than that of a C—H bond. In a group of bonds with similar bond energies, the *frequency decreases with increasing atomic weight.*

Stronger bonds are generally stiffer, requiring more force to stretch or compress them. Thus, stronger bonds usually vibrate faster than weaker bonds (assuming the atoms have similar masses). For example, O—H bonds are stronger than C—H bonds, and O—H bonds vibrate at higher frequencies. Triple bonds are stronger than double bonds, so triple bonds vibrate at higher frequencies than double bonds. Similarly, double bonds vibrate at higher frequencies than single bonds. In a group of bonds having atoms of similar masses, the *frequency increases with bond energy.*

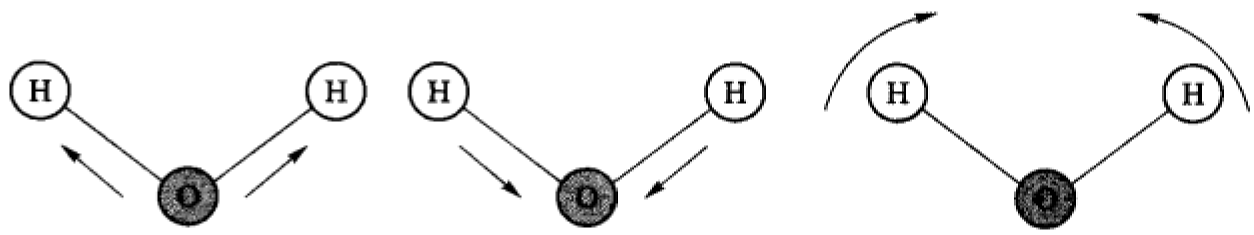
Table 12−1 lists some common types of bonds, together with their stretching frequencies to show how frequency varies with the masses of the atoms and the strength of the bonds.

TABLE 12−1 Bond Stretching Frequencies

In a group of bonds with similar bond energies, *the frequency decreases with increasing atomic weight.* In a group of bonds between similar atoms, the *frequency increases with bond energy.* The bond energies and frequencies listed here are approximate.

Bond	Bond Energy/kJ	Stretching Frequency/cm^{-1}
	Frequency decreases with increasing atomic mass	
C—H ↓ heavier atoms	420	3 000 ↓ σ decreases
C—D	420	2 100
C—C	350	1 200
	Frequency increases with bond energy	
C—C	350 ↓ stronger bond	1 200 ↓ σ increases
C=C	611	1 660
C≡C	840	2 200
C—N	305 ↓	1 200 ↓
C=N	615	1 650
C≡N	891	2 200
C—O	360 ↓	1 100 ↓
C=O	745	1 700

Consider the fundamental vibrational modes of a water molecule in the following diagram. The two O—H bonds can stretch in phase with each other (**symmetric stretching**), or they can stretch out of phase (**antisymmetric stretching**). The H—O—H bond angle can also change in a bending vibration, making a **scissoring** motion.



symmetric stretching（对称伸缩）　　antisymmetric stretching（不对称伸缩）　　bending (scissoring)（弯曲或剪式振动）

A nonlinear molecule with n atoms generally has $3n-6$ fundamental vibrational modes. Water (3 atoms) has $3(3)-6=3$ fundamental modes, as shown in the preceding figure. Methanol has $3(6)-6=12$ fundamental modes, and ethanol has $3(9)-6=21$ fundamental modes. We also observe combinations and multiples (overtones) of these simple fundamental vibrational modes. As you can see, the number of absorptions in an infrared spectrum can be quite large, even for simple molecules.

It is highly unlikely that the IR spectra of two different compounds (except enantiomers) will show the same frequencies for all their various complex vibrations. For this reason, the infrared spectrum provides a "fingerprint" of a molecule. In fact, the region of the IR spectrum containing most of these complex vibrations (600 to 1 400 cm^{-1}) is commonly called the **fingerprint region** of the spectrum.

The simple stretching vibrations in the 1 600 to 3 500 cm^{-1} region are the most characteristic and predictable; our study of infrared spectroscopy will concentrate on them. Although our introductory study of IR spectra will largely ignore bending vibrations, you should remember that these absorptions generally appear in the 600 to 1 400 cm^{-1} region of the spectrum.

12−5 IR-Active and IR-Inactive Vibrations

Not all molecular vibrations absorb infrared radiation. To understand which ones do and which do not, we need to consider how an electromagnetic field interacts with a molecular bond. The key to this interaction lies with the polarity of the bond, measured as its dipole moment. A bond with a dipole moment can be visualized as a positive charge and a negative charge separated by a spring. If this bond is placed in an electric field (Figure 12−2), it is either stretched or compressed, depending on the direction of the field.

One of the components of an electromagnetic wave is a rapidly reversing electric field ($\vec{E}$). This field alternately stretches and compresses a polar bond, as shown in Figure 12−2. When the electric field is in the same direction as the dipole moment, the bond is compressed and its dipole moment decreases. When the field is opposite the dipole moment, the bond stretches and its dipole moment increases. If this alternate stretching and compressing of the bond occurs at the frequency of the molecule's natural rate of vibration, energy may be absorbed. Vibrations of bonds with dipole moments generally result in IR absorptions and are said to be **IR active.**

If a bond is symmetrical and has zero dipole moment, the electric field does not interact with the bond. For example, the triple bond of acetylene (H—C≡C—H) has zero dipole moment, and the dipole moment remains zero if the bond is stretched or compressed. Because the vibration produces no change in the dipole moment, there is no absorption of energy. This vibration is said to be **IR inactive**, and it produces no absorption in the IR spectrum. The key to an IR-active vibration is that *the vibration must change the dipole moment of the molecule.*

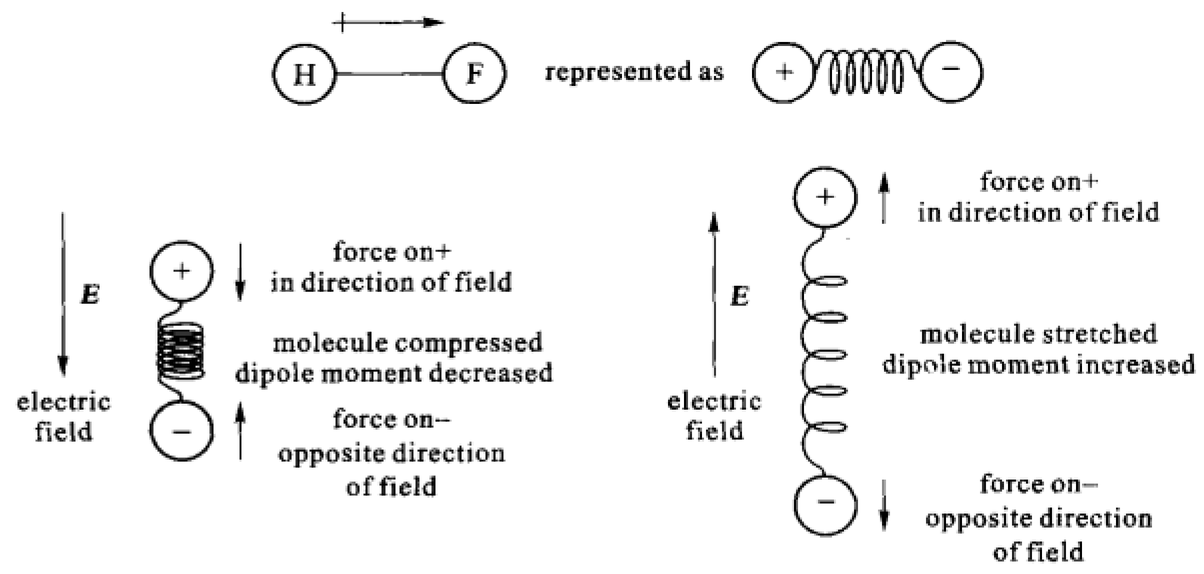
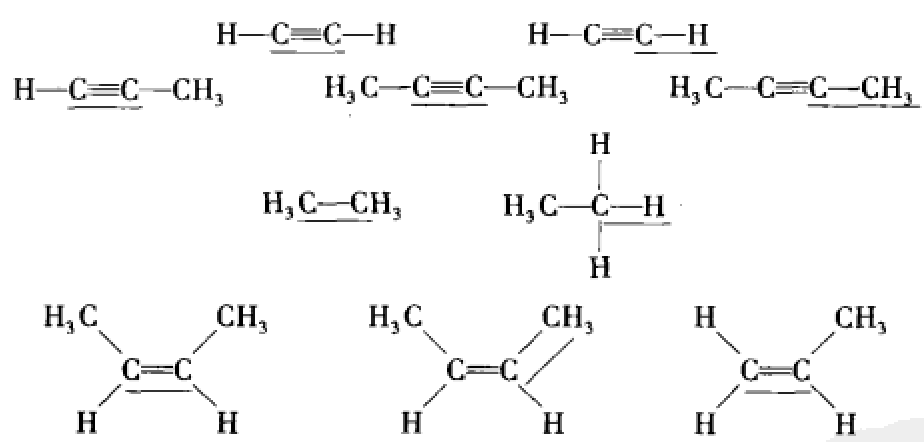


Figure 12−2 Effect of an electric field on a polar bond. A bond with a dipole moment (as in HF, for example) is either stretched or compressed by an electric field, depending on the direction of the field. Notice that the force on the positive charge is in the direction of the electric field ($\vec{E}$), and the force on the negative charge is in the opposite direction.

In general, if a bond has a dipole moment, its stretching frequency causes an absorption in the IR spectrum. If a bond is symmetrically substituted and has zero dipole moment, its stretching vibration is weak or absent in the spectrum. Bonds with zero dipole moments sometimes produce absorptions (usually weak) because molecular collisions, rotations, and vibrations make them unsymmetrical part of the time.

PROBLEM 12−1

Which of the bonds designated are expected to have IR-active stretching frequencies?



12−6 Measurement of the IR Spectrum

Infrared spectra can be measured using liquid, solid, or gaseous samples that are placed in the beam of infrared light. A drop of a liquid can be placed as a thin film between two salt plates made of NaCl or KBr, which are transparent to infrared light at most important frequencies. A solid can be ground with KBr and pressed into a disk that is placed in the light beam. Alternatively, a solid sample can be ground into a pasty *mull* with paraffin oil. As with a liquid, the mull is placed between two salt plates. Solids can also be dissolved in common solvents such as CH_2Cl_2, CCl_4, or CS_2 that do not have absorptions in the areas of interest. Gases are placed in a longer

cell with polished salt windows. These *gas cells* often contain mirrors that reflect the beam through the cell several times for stronger absorption.

A **Fourier transform infrared spectrometer** (**FT-IR**) uses an **interferometer**, like that shown in Figure 12-3, to measure an IR spectrum. The infrared light goes from the glowing source to a beamsplitter, usually made of polished KBr, placed at a 45° angle. Part of the beam passes through the beamsplitter, and part is reflected at a right angle. The reflected beam strikes a stationary mirror, while the transmitted beam strikes a mirror that moves at a constant speed. The beams return from the mirrors to recombine at the beamsplitter. The beam from the moving mirror has traveled a different distance than the beam from the fixed mirror, and the two beams combine to create an interference pattern called an **interferogram**. This interferogram, which simultaneously contains all frequencies, passes through the sample compartment to reach the detector.

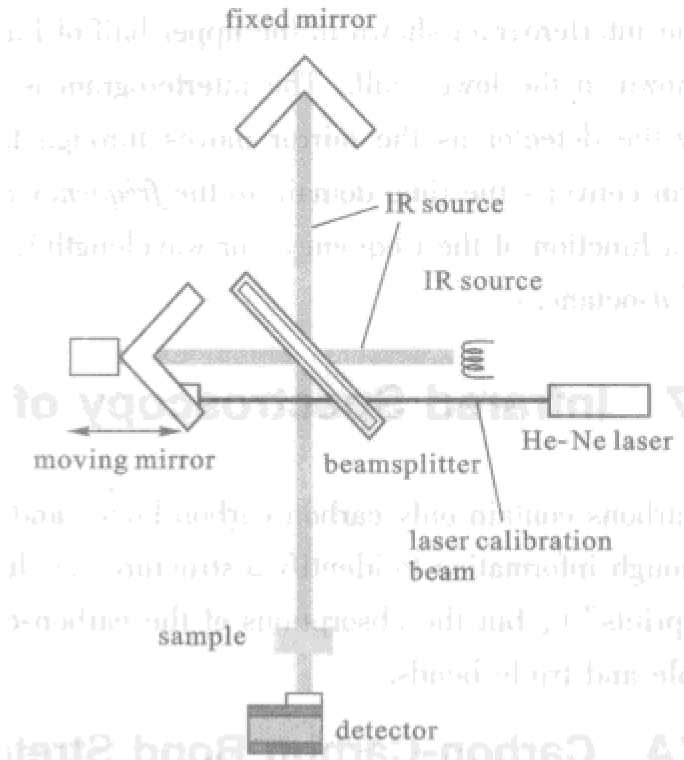


Figure 12-3 Block diagram of an interferometer in an FT-IR spectrometer. The light beams reflected from the fixed and moving mirrors are combined to form an interferogram, which passes through the sample to enter the detector.

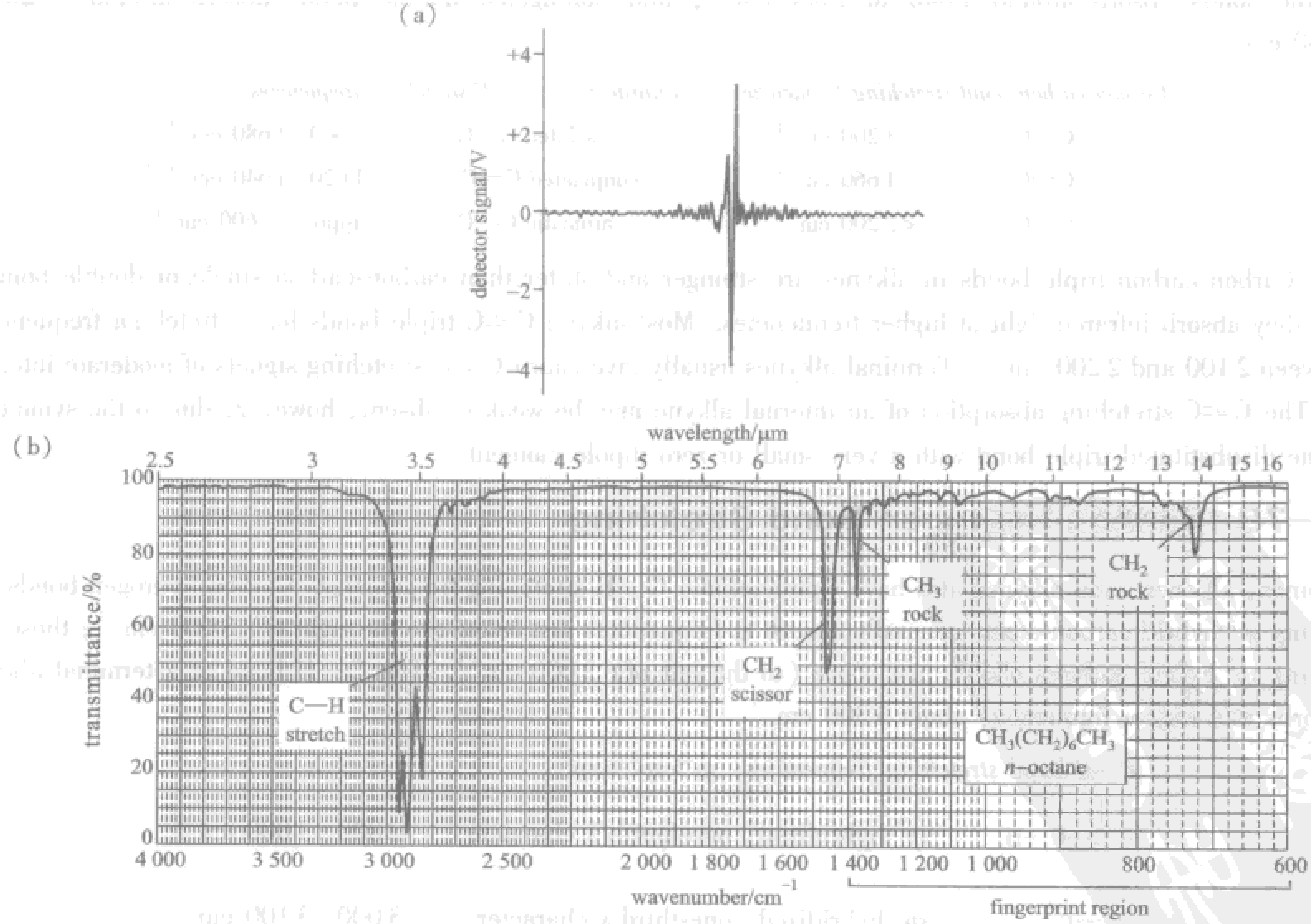


Figure 12-4 (a) Interferogram generated by *n*-octane. (b) Infrared spectrum of *n*-octane. Notice that the frequencies shown in a routine IR spectrum range from about 600 cm^{-1} to about 4 000 cm^{-1}.

The interferogram shown in the upper half of Figure 12−4 contains all the information contained in the spectrum shown in the lower half. The interferogram is said to be in the *time domain*, corresponding to the energy seen by the detector as the mirror moves through the signal. A standard computer algorithm called a Fourier transform converts the time domain to the *frequency domain* spectrum that allows us to see the strength of absorption as a function of the frequency (or wavelength). Figure 12−4 shows both the interferogram and the IR spectrum of *n*-octane.

12−7 Infrared Spectroscopy of Hydrocarbons

Hydrocarbons contain only carbon-carbon bonds and carbon-hydrogen bonds. An infrared spectrum does not provide enough information to identify a structure conclusively (unless an authentic spectrum is available to compare "fingerprints"), but the absorptions of the carbon-carbon and carbon-hydrogen bonds can indicate the presence of double and triple bonds.

12−7A Carbon-Carbon Bond Stretching

Stronger bonds generally absorb at higher frequencies because of their greater stiffness. Carbon-carbon single bonds absorb around 1 200 cm^{-1}, C═C double bonds absorb around 1 660 cm^{-1}, and C≡C triple bonds absorb around 2 200 cm^{-1}.

The absorptions of C═C double bonds are useful for structure determination. Most unsymmetrically substituted double bonds produce observable stretching absorptions in the region of 1 600 to 1 680 cm^{-1}. Isolated double bonds absorb around 1 640 to 1 680 cm^{-1}, and conjugated double bonds absorb around 1 620 to 1 640 cm^{-1}.

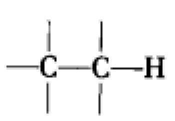
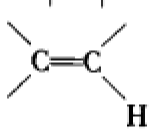
Carbon-carbon bond stretching frequencies		*Characteristic C═C stretching frequencies*	
C—C	1 200 cm^{-1}	isolated C═C	1 640−1 680 cm^{-1}
C═C	1 660 cm^{-1}	conjugated C═C	1 620−1 640 cm^{-1}
C≡C	<2 200 cm^{-1}	aromatic C═C	approx. 1 600 cm^{-1}

Carbon-carbon triple bonds in alkynes are stronger and stiffer than carbon-carbon single or double bonds, and they absorb infrared light at higher frequencies. Most alkyne C≡C triple bonds have stretching frequencies between 2 100 and 2 200 cm^{-1}. Terminal alkynes usually give sharp C≡C stretching signals of moderate intensity. The C≡C stretching absorption of an internal alkyne may be weak or absent, however, due to the symmetry of the disubstituted triple bond with a very small or zero dipole moment.

12−7B Carbon-Hydrogen Bond Stretching

Alkanes, alkenes, and alkynes also have characteristic C—H stretching frequencies. Carbon-hydrogen bonds involving sp^3 hybrid carbon atoms generally absorb at frequencies just *below* (to the right of) 3 000 cm^{-1}; those involving sp^2 hybrid carbons absorb just *above* (to the left of) 3 000 cm^{-1}. The C—H bond of a terminal alkyne absorbs at a higher frequency: about 3 300 cm^{-1}.

C—H bond stretching frequencies: $sp > sp^2 > sp^3$

	sp^3 hybridized, one-fourth *s* character	2 800−3 000 cm^{-1}
	sp^2 hybridized, one-third *s* character	3 000−3 100 cm^{-1}
—C≡C—H	*sp* hybridized, one-half *s* character	3 300 cm^{-1}

12-8 Characteristic Absorptions of Alcohols and Amines

The O—H bonds of alcohols and the N—H bonds of amines are strong and stiff. The vibration frequencies of O—H and N—H bonds therefore occur at higher frequencies than those of most C—H bonds (except for alkynyl ≡C—H bonds).

O—H and N—H stretching frequencies

alcohol O—H	3 300 cm^{-1}, broad
acid O—H	3 000 cm^{-1}, broad
amine N—H	3 300 cm^{-1}, broad with spikes

Alcohol O—H bonds absorb over a wide range of frequencies, centered around 3 300 cm^{-1}. Alcohol molecules are involved in hydrogen bonding, with different molecules having different instantaneous arrangements. The O—H stretching frequencies reflect this diversity of hydrogen-bonding arrangements, resulting in very broad absorptions.

Amine N—H bonds also have stretching frequencies in the 3 300 cm^{-1} region, or even slightly higher. Like alcohols, amines participate in hydrogen bonding that can broaden the N—H absorptions. With amines, however, the absorption is somewhat weaker, and there may be one or more sharp spikes superimposed on the broad N—H stretching absorption: often one N—H spike for a secondary amine (R_2NH) and two N—H spikes for a primary amine (RNH_2). These sharp spikes, combined with the presence of nitrogen in the molecular formula, help to distinguish amines from alcohols.

12-9 Characteristic Absorptions of Carbonyl Compounds

12-9A Simple Ketones, Aldehydes, and Acids

The C=O stretching vibrations of simple ketones, aldehydes, and carboxylic acids occur at frequencies around 1 710 cm^{-1}. These frequencies are higher than those for C=C double bonds because the C=O double bond is stronger and stiffer. Some carbonyl groups absorb at frequencies *higher* than 1 710 cm^{-1}. For example, simple carboxylic esters absorb around 1 735 cm^{-1}. These higher-frequency absorptions are also seen in strained cyclic ketones (in a five-membered ring or smaller).

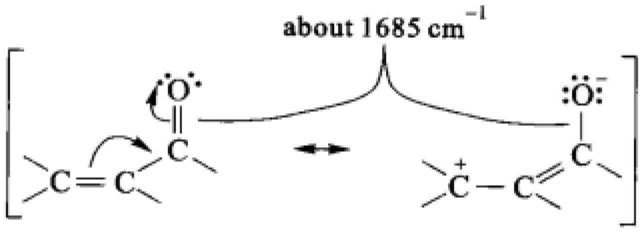
In addition to the strong C=O stretching absorption, an aldehyde shows a characteristic set of two low-frequency C—H stretching frequencies around 2 700 and 2 800 cm^{-1}. Neither a ketone nor an acid produces these absorptions.

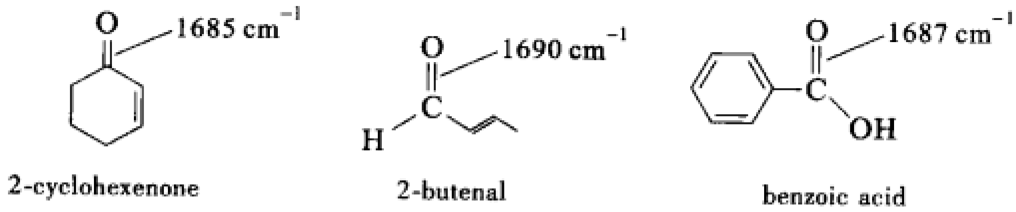
A carboxylic acid produces a characteristic broad O—H absorption in addition to the intense carbonyl stretching absorption. Because of the unusually strong hydrogen bonding in carboxylic acids, the broad O—H stretching frequency is shifted to about 3 000 cm^{-1}, centered on top of the usual C—H absorption. This broad O—H absorption gives a characteristic overinflated shape to the peaks in the C—H stretching region. Participation of the acid carbonyl group in hydrogen bonding frequently results in broadening of the strong carbonyl absorption as well.

12-9B Resonance Lowering of Carbonyl Frequencies

In Section 12-7A we saw that conjugation of a C=C double bond lowers its stretching frequency. This is also

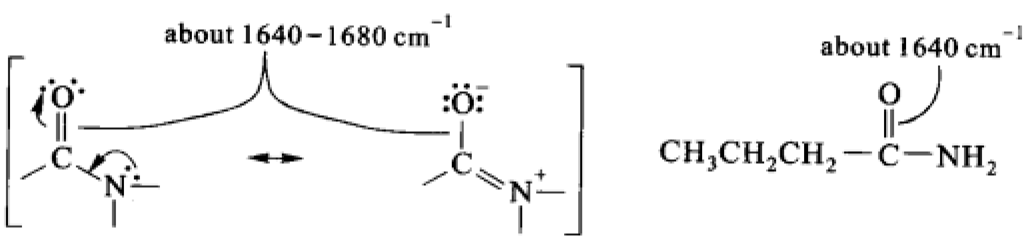
true of conjugated carbonyl groups, as shown next. Delocalization of the pi electrons reduces the electron density of the carbonyl double bond, weakening it and lowering the stretching frequency from about 1 710 cm^{-1} to about 1 685 cm^{-1} for conjugated ketones, aldehydes, and acids.





The C═C absorption of a conjugated carbonyl compound may not be apparent in the IR spectrum because it is so much weaker than the C═O absorption. The presence of the C═C double bond is often inferred from its effect on the C═O frequency and the presence of unsaturated ═C—H absorptions above 3 000 cm^{-1}.

The carbonyl groups of amides absorb at particularly low IR frequencies: about 1 640 to 1 680 cm^{-1}. The dipolar resonance structure (shown next) places part of the pi bond between carbon and nitrogen, leaving less than a full C═O double bond.



Like primary amines, most primary amides show two spikes in the N—H stretching region (about 3 300 cm^{-1}). Secondary amides (like secondary amines) generally show one N—H spike.

12–10 Characteristic Absorptions of C—N Bonds

Infrared absorptions of carbon-nitrogen bonds are similar to those of carbon-carbon bonds, except that carbon-nitrogen bonds are more polar and give stronger absorptions. Carbon-nitrogen single bonds absorb around 1 200 cm^{-1}, in a region close to many C—C and C—O absorptions. Therefore, the C—N single bond stretch is rarely useful for structure determination.

Carbon-nitrogen double bonds absorb in the same region as C═C double bonds, around 1 660 cm^{-1}; however, the C═N bond gives rise to stronger absorptions because of its greater dipole moment. The C═N stretch often resembles a carbonyl absorption in intensity.

The most readily recognized carbon-nitrogen bond is the triple bond of a nitrile. The stretching frequency of the nitrile C≡N bond is close to that of an acetylenic C≡C triple bond, about 2 200 cm^{-1}; however, nitriles generally absorb *above* 2 200 cm^{-1} (2 200 to 2 300 cm^{-1}), while alkynes absorb *below* 2 200 cm^{-1}. Also, nitrile triple bonds are more polar than C≡C triple bonds, so nitriles usually produce stronger absorptions than alkynes.

C—N bond stretching frequencies

C—N	1 200 cm^{-1}	usually strong
C═N	1 660 cm^{-1}	usually strong
C≡N	>2 200 cm^{-1}	usually strong
for comparison: C≡C	<2 200 cm^{-1}	(usually moderate or weak)

12−11 Simplified Summary of IR Stretching Frequencies

It may seem there are too many numbers to memorize in infrared spectroscopy. There are hundreds of characteristic absorptions for different kinds of compounds. For everyday use, we can get by with only a few stretching frequencies, shown in Table 12−2. In using this table, remember that the numbers are approximate and they do not give ranges to cover all the unusual cases. Also, remember how frequencies change as a result of conjugation, ring strain, and other factors.

TABLE 12−2 Summary of IR Stretching Frequencies

Frequency/cm^{-1}	Functional Group		Comments
3 300	alcohol	O—H	always broad
	amine, amide	N—H	may be broad, sharp, or broad with spikes
	alkyne	≡C—H	always sharp, usually strong
3 000	alkane	—C—H (sp³)	just below 3 000 cm^{-1}
	alkene	=C—H	just above 3 000 cm^{-1}
	acid	O—H	very broad
2 200	alkyne	—C≡C—	just below 2 200 cm^{-1}
	nitrile	—C≡N	just above 2 200 cm^{-1}
1 710 (very strong)	carbonyl	>C═O	ketones, aldehydes, acids esters higher, about 1 735 cm^{-1} conjugation lowers frequency amides lower, about 1 650 cm^{-1}
1660	alkene	>C═C<	conjugation lowers frequency aromatic C═C about 1 600 cm^{-1}
	imine	>C═N—	stronger than C═C
	amide	>C═O	stronger than C═C (see above)

Ethers, esters, and alcohols also show C—O stretching between 1 000 and 1 200 cm^{-1}.

Strengths and Limitations of Infrared Spectroscopy The most useful aspect of infrared spectroscopy is its ability to identify functional groups, but IR does not provide much information about the carbon skeleton or the alkyl groups in the compound. These aspects of the structure are more easily determined by NMR, as we will see in Chapter 13. Even an expert spectroscopist can rarely determine a structure based only on the IR spectrum.

Ambiguities often arise in the interpretation of IR spectra. For example, a strong absorption at 1 680 cm^{-1} might arise from an amide, an isolated double bond, a conjugated ketone, a conjugated aldehyde, or a conjugated carboxylic acid. Familiarity with other regions of the spectrum usually enables us to determine which of these functional groups is present. In some cases, we cannot be entirely certain of the functional group without additional information, usually provided by other types of spectroscopy.

Infrared spectroscopy *can* provide conclusive proof that two compounds are either the same or different. The peaks in the fingerprint region depend on complex vibrations involving the entire molecule, and it is impossible for any two compounds (except enantiomers) to have precisely the same infrared spectrum.

To summarize, an infrared spectrum is valuable in three ways:

1. It indicates the functional groups in the compound.
2. It shows the *absence* of other functional groups that would give strong absorptions if they were present.
3. It can confirm the identity of a compound by comparison with a known sample.

SOLVED PROBLEM 12-1

You have an unknown with an absorption at 1 680 cm^{-1}; it might be an amide, an isolated double bond, a conjugated ketone, a conjugated aldehyde, or a conjugated carboxylic acid. Describe what spectral characteristics you would look for to help you determine which of these possible functional groups might be causing the 1 680 peak.

SOLUTION

Amide: (1 680 peak is strong) Look for N—H absorptions (with spikes) around 3 300 cm^{-1}.

Isolated double bond: (1 680 peak is weak or moderate) Look for =C—H absorptions just above 3 000 cm^{-1}.

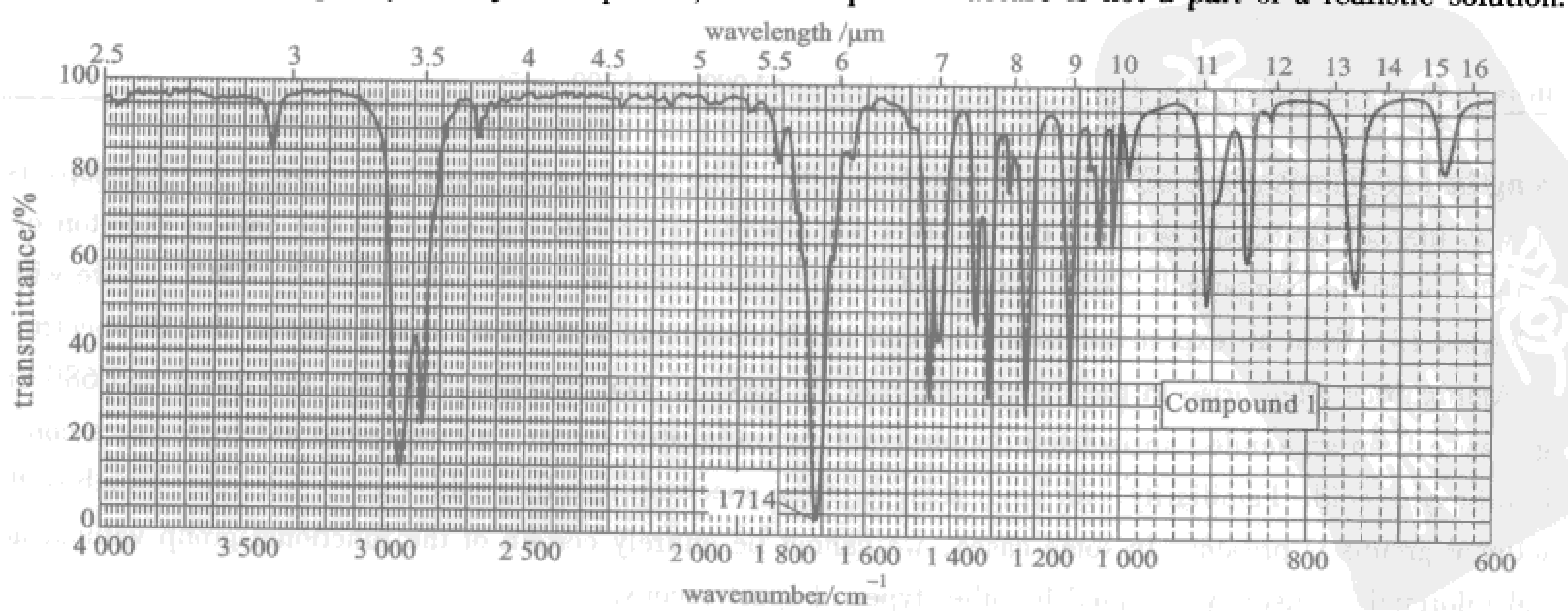
Conjugated ketone: (1 680 peak is strong) There must be a double bond nearby, conjugated with the C=O, to lower the C=O frequency to 1 680 cm^{-1}. Look for the C=C of the nearby double bond (moderate, 1 620 to 1 640 cm^{-1}) and its =C—H above 3 000 cm^{-1}.

Conjugated aldehyde: (1 680 peak is strong) Look for the aldehyde C—H stretch about 2 700 and 2 800 cm^{-1}. Also look for the C=C and C—H of the nearby double bond (1 620 to 1 640 cm^{-1} and just above 3 000 cm^{-1}).

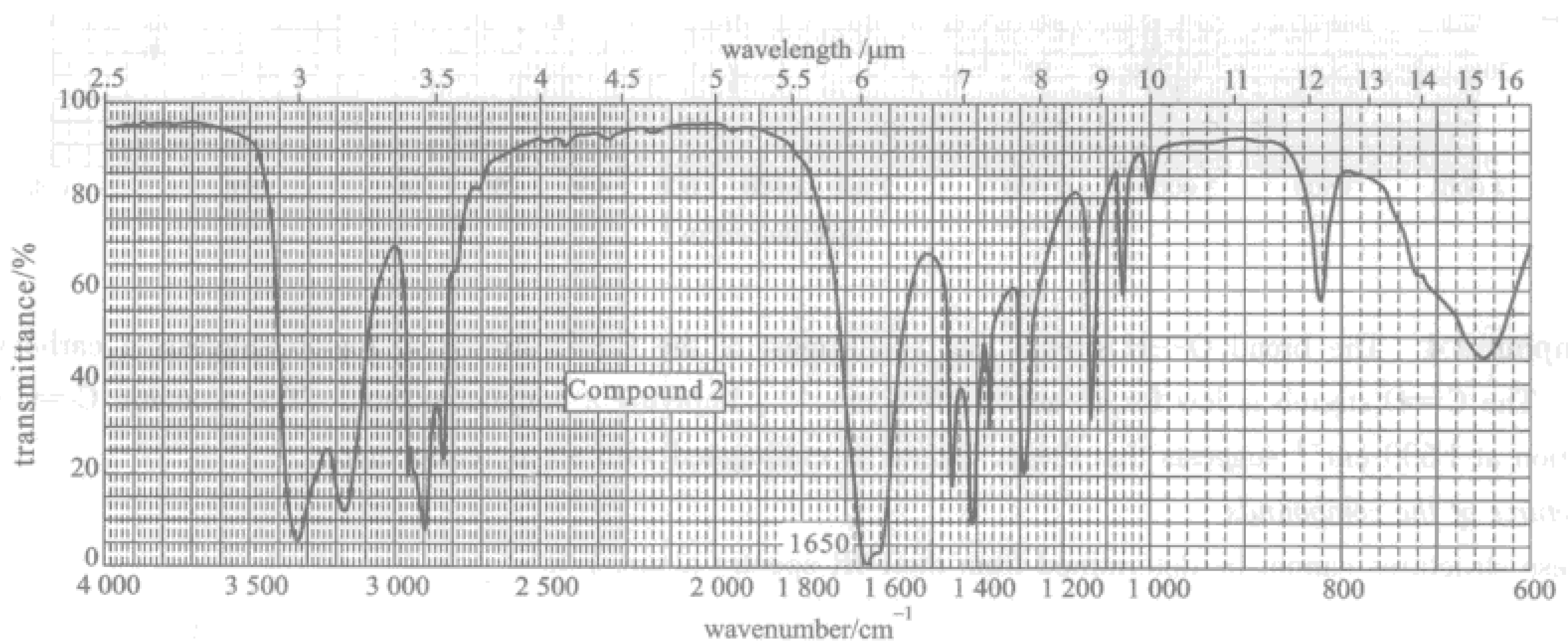
Conjugated carboxylic acid: (1 680 peak is strong) Look for the characteristic acid O—H stretch centered *on top of* the C—H stretch around 3 000 cm^{-1}. Also look for the C=C and =C—H of the nearby double bond (1 620 to 1 640 cm^{-1} and just above 3 000 cm^{-1}).

12-12 Reading and Interpreting IR Spectra

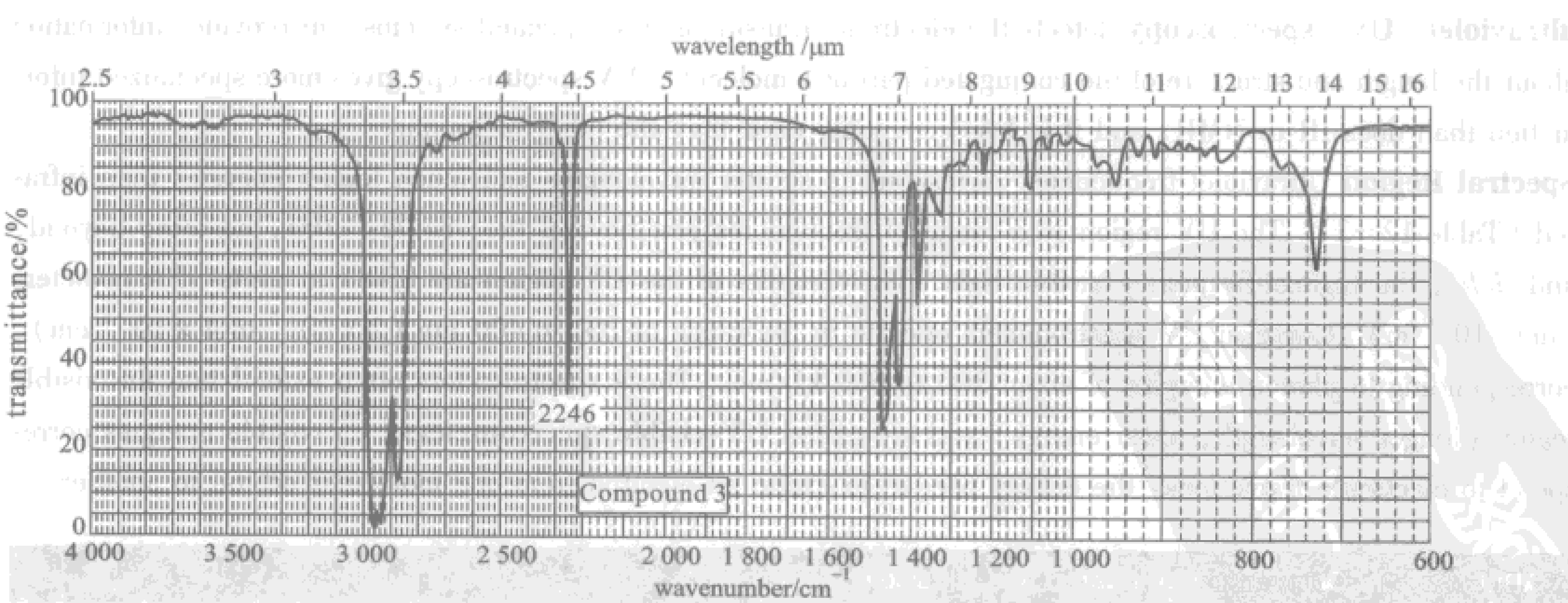
Study this section by looking at each spectrum and writing down the important frequencies and your proposed functional groups. Then look at the solution and compare it with your solution. The actual structures of these compounds are shown at the end of this section. They are not given with the solutions because *you cannot determine these structures using only the infrared spectra*, so a complete structure is not a part of a realistic solution.



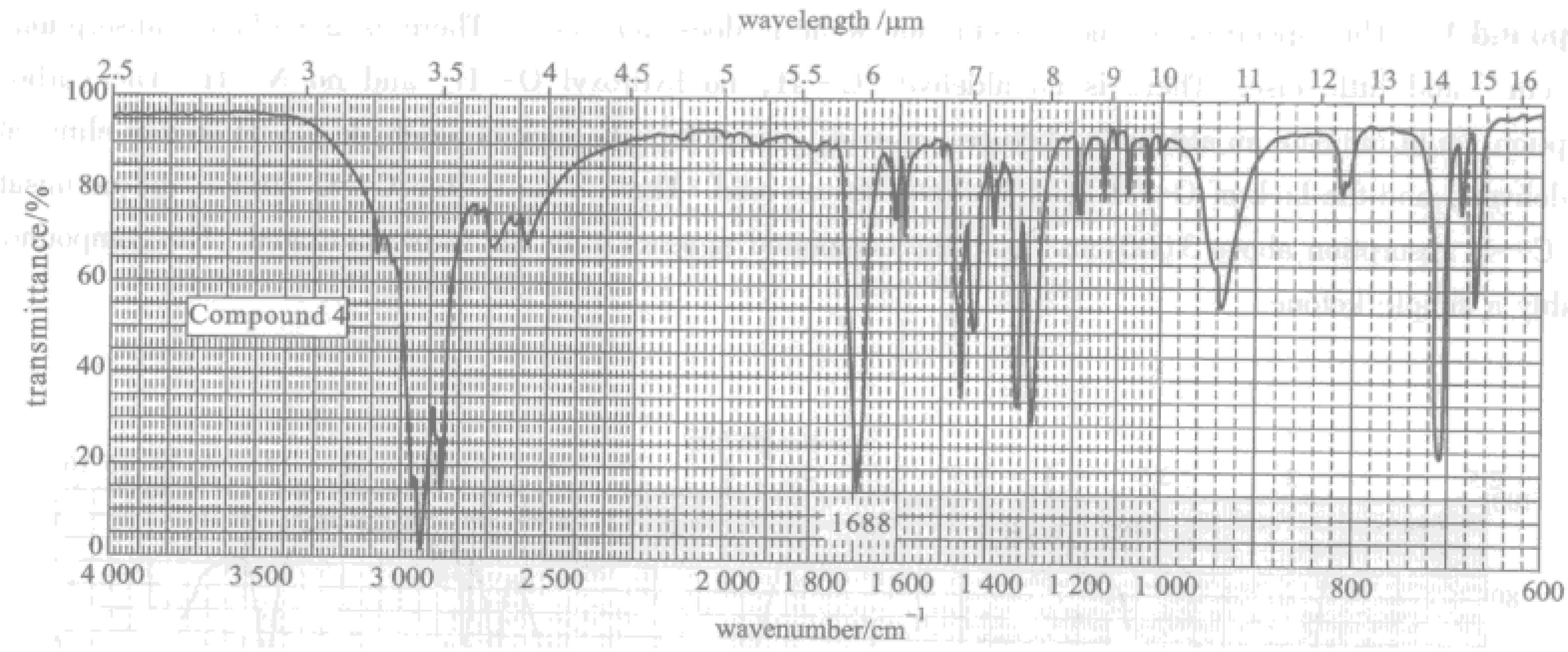
Compound 1 This spectrum is most useful for what it does *not* show. There is a carbonyl absorption at 1 714 cm^{-1} and little else. There is no aldehyde C—H, no hydroxyl O—H, and no N—H. The carbonyl absorption could indicate an aldehyde, ketone, or acid, except that the lack of aldehyde C—H stretch eliminates an aldehyde, and the lack of O—H stretch eliminates an acid. There is no visible C═C stretch and no unsaturated C—H absorption above 3 000 cm^{-1}, so the compound appears to be otherwise saturated. The compound is probably a simple ketone.



Compound 2 The absorption at 1 650 cm^{-1} is so intense that it probably indicates a carbonyl group. A carbonyl group at this low frequency suggests an amide. The doublet (a pair of peaks) of N—H absorption around 3 300 cm^{-1} also suggests a primary amide, R—$CONH_2$. Since there is no C—H absorption above 3 000 cm^{-1}, this is probably a saturated amide.



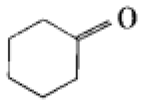
Compound 3 The sharp peak at 2 246 cm^{-1} results from a nitrile C≡N stretch. (An alkyne C≡C absorption would be weaker and below 2 200 cm^{-1}.) The absence of C═C stretch or C—H stretch above 3 000 cm^{-1} suggests that the nitrile is otherwise saturated.



Compound 4 The broad O—H stretch that spans most of the C—H stretching region suggests a carboxylic acid. The C=O stretch is low for an acid (1 688 cm^{-1}), implying a conjugated acid. The aromatic C=C absorption at 1 600 cm^{-1} suggests that the acid may be conjugated with an aromatic ring.

Structures of the compounds

(These structures cannot be determined from their IR spectra alone.)



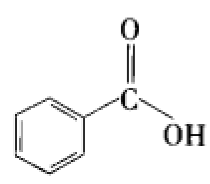
compound 1

$CH_3CH_2—C(=O)—NH_2$

compound 2

$CH_3(CH_2)_4—C≡N$

compound 3



compound 4

12−13 Ultraviolet Absorption Spectroscopy

ultraviolet (UV) spectroscopy detects the electronic transitions of conjugated systems and provides information about the length and structure of the conjugated part of a molecule. UV spectroscopy gives more specialized information than does IR or NMR, and it is less commonly used than the other techniques.

Spectral Region Ultraviolet frequencies correspond to shorter wavelengths and much higher energies than infrared (Table 12−3). The UV region is a range of frequencies just beyond the visible: *ultra*, meaning beyond, and *violet*, the highest-frequency visible light. Wavelengths of the UV region are given in units of nanometers (nm; 10^{-9} m). Common UV spectrometers operate in the range of 200 to 400 nm (2×10^{-5} to 4×10^{-5} cm), corresponding to photon energies of about 300 to 600 kJ/mol. These spectrometers often extend into the visible region (longer wavelength, lower energy) and are called **UV-visible spectrometers**. UV-visible energies correspond to electronic transitions: the energy needed to excite an electron from one molecular orbital to another.

TABLE 12−3 Comparison of Infrared and Ultraviolet Wavelengths

Spectral Region	Wavelength (λ)	Energy Range/($kJ \cdot mol^{-1}$)
ultraviolet	200−400 nm [$(2-4) \times 10^{-5}$ cm]	300−600
visible	400−800 nm [$(4-8) \times 10^{-5}$ cm]	150−300
infrared	2.5−25 μm [$(2.5-25) \times 10^{-4}$ cm]	4.6−46

12−14 Ultraviolet Light and Electronic Transitions

The wavelengths of UV light absorbed by a molecule are determined by the electronic energy differences between orbitals in the molecule. Sigma bonds are very stable, and the electrons in sigma bonds are usually unaffected by wavelengths of light above 200 nm. Pi bonds have electrons that are more easily excited into higher energy orbitals. Conjugated systems are particularly likely to have low-lying vacant orbitals, and electronic transitions into these orbitals produce characteristic ultraviolet absorptions.

Ethylene, for example, has two pi orbitals: the bonding orbital (π, the HOMO) and the antibonding orbital (π^*, the LUMO). The ground state has two electrons in the bonding orbital and none in the antibonding orbital. A photon with the right amount of energy can excite an electron from the bonding orbital (π) to the antibonding orbital (π^*). This transition from a π bonding orbital to a π^* antibonding orbital is called a $\pi \rightarrow \pi^*$ *transition.*

The $\pi \rightarrow \pi^*$ transition of ethylene requires absorption of light at 171 nm (686 kJ/mol). Most UV spectrometers cannot detect this absorption because it is obscured by the absorption caused by oxygen in the air. In conjugated systems, however, there are electronic transitions with lower energies that correspond to wavelengths longer than 200 nm. Figure 12−5 compares the MO energies of ethylene with those of butadiene to show that the HOMO and LUMO of butadiene are closer in energy than those of ethylene. The HOMO of butadiene is higher in energy than the HOMO of ethylene, and the LUMO of butadiene is lower in energy than the LUMO of ethylene. Both differences reduce the relative energy of the $\pi_2 \rightarrow \pi_3^*$ transition. The resulting absorption is at 217 nm (540 kJ/mol), which can be measured using a standard UV spectrometer.

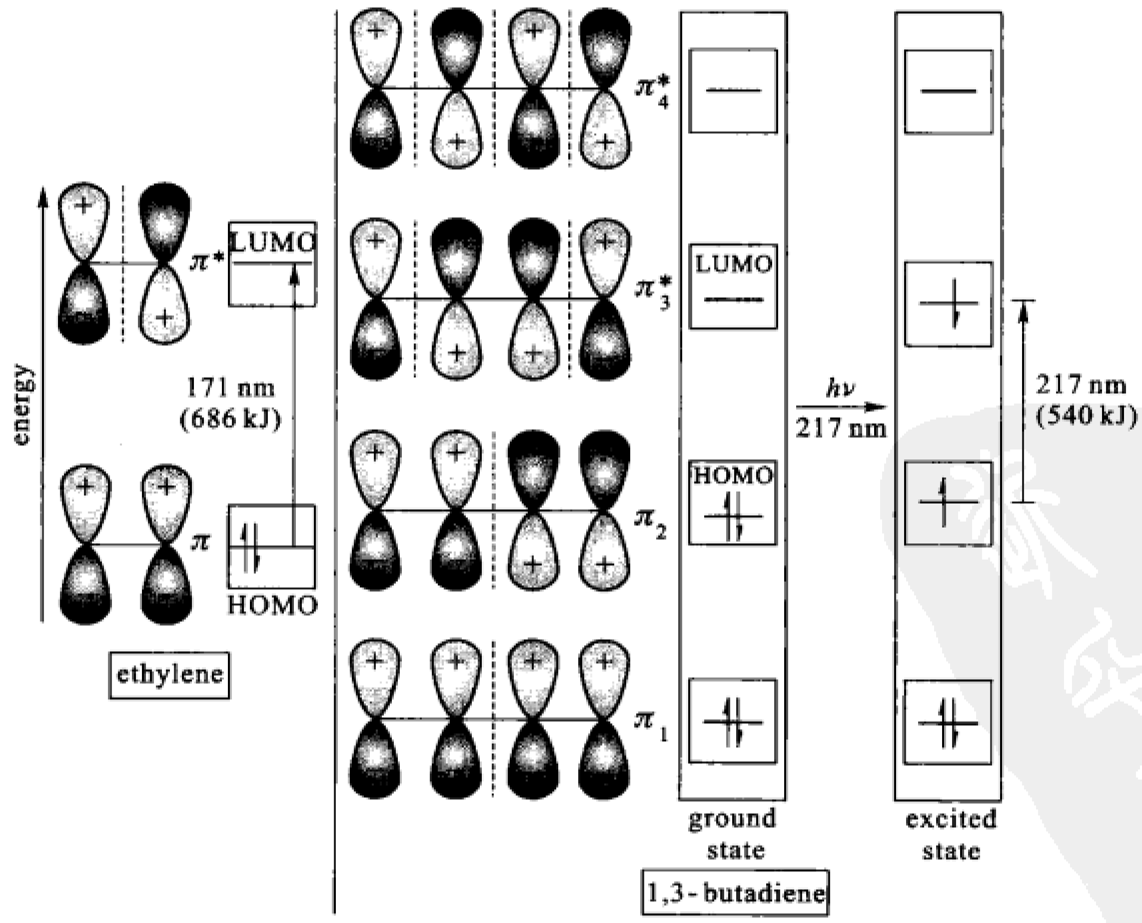
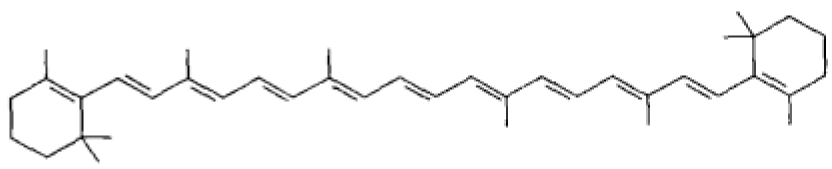


Figure 12−5 Comparison of HOMO-LUMO energy differences. In 1,3-butadiene, the $\pi \rightarrow \pi^*$ transition absorbs at a wavelength of 217 nm (540 kJ/mol) compared with 171 nm (686 kJ/mol) for ethylene. This longer wavelength (lower-energy) absorption results from a smaller energy difference between the HOMO and LUMO in butadiene than in ethylene.

Just as conjugated dienes absorb at longer wavelengths than simple alkenes, conjugated trienes absorb at even longer wavelengths. In general, the energy difference between HOMO and LUMO decreases as the length of conjugation increases. The principal $\pi \rightarrow \pi^*$ transition in 1,3,5-hexatriene occurs at 258 nm (452 kJ/mol).

We can summarize the effects of conjugation on the wavelength of UV absorption by stating a general rule: *A compound that contains a longer chain of conjugated double bonds absorbs light at a longer wavelength.* β-Carotene, which has 11 conjugated double bonds in its pi system, absorbs at 454 nm, well into the visible region of the spectrum, corresponding to absorption of blue light. White light from which blue has been removed appears orange. β-Carotene is the principal compound responsible for giving carrots their orange color. Carotene derivatives provide many of the colors we see in fruits, vegetables, and autumn leaves.



β-carotene (β-胡萝卜素)

Because they have no interaction with each other, isolated double bonds do not contribute to shifting the UV absorption to longer wavelengths. Both their reactions and their UV absorptions are like those of simple alkenes. For example, 1,4-pentadiene absorbs at 178 nm, a value that is typical of simple alkenes rather than conjugated dienes.

12-15 Measurement of the UV-Visible Spectrum

To measure the ultraviolet (or UV-visible) spectrum of a compound, the sample is dissolved in a solvent (often ethanol) that does not absorb above 200 nm. The sample solution is placed in a quartz cell, and some of the solvent is placed in a **reference cell**. An ultraviolet spectrometer operates by comparing the amount of light transmitted through the sample (the **sample beam**) with the amount of light in the **reference beam**. The reference beam passes through the reference cell to compensate for any absorption of light by the cell and the solvent.

The spectrometer (Figure 12-6) has a *source* that emits all frequencies of UV light (above 200 nm). This light passes through a *monochromator*, which uses a diffraction grating or a prism to spread the light into a spectrum and select one wavelength. This single wavelength of light is split into two beams, with one beam passing through the sample cell and the other passing through the reference (solvent) cell. The detector continuously measures the intensity ratio of the reference beam (I_r) compared with the sample beam (I_s). As the spectrometer scans the wavelengths in the UV region, a printer draws a graph (called a *spectrum*) of the absorbance of the sample as a function of the wavelength.

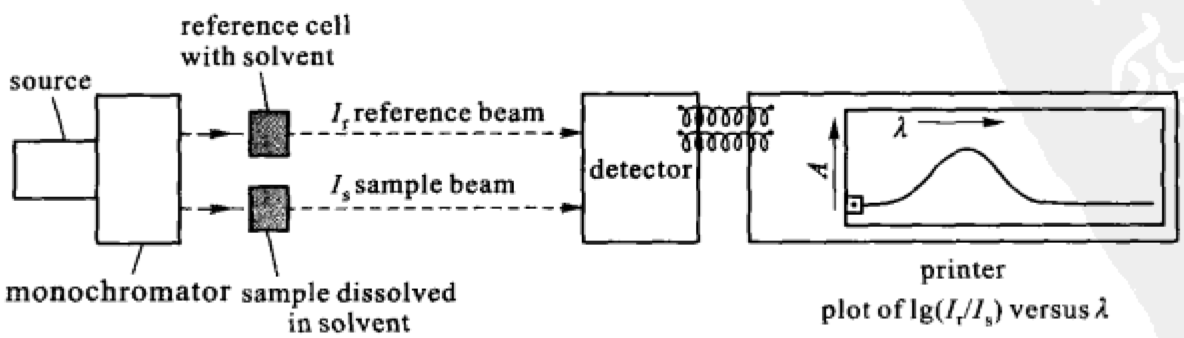


Figure 12-6 Diagram of an ultraviolet spectrometer. In the ultraviolet spectrometer, a monochromator selects one wavelength of light, which is split into two beams. One beam passes through the sample cell, while the other passes through the reference cell. The detector measures the ratio of the two beams, and the printer plots this ratio as a function of wavelength.

The *absorbance*, A, of the sample at a particular wavelength is governed by *Beer's law.*

$$A = \lg\left(\frac{I_r}{I_s}\right) = \kappa c l$$

where

c = sample concentration in moles per liter

l = path length of light through the cell in centimeters

κ = the **molar absorptivity** (or **molar extinction coefficient**) of the sample

Molar absorptivity (κ) is a measure of how strongly the sample absorbs light at that wavelength.

If the sample absorbs light at a particular wavelength, the sample beam (I_s) is less intense than the reference beam (I_r), and the ratio I_r/I_s is greater than 1. The ratio is equal to 1 when there is no absorption. The absorbance (the logarithm of the ratio) is therefore greater than zero when the sample absorbs, and is equal to zero when it does not. A UV spectrum is a plot of A, the absorbance of the sample, as a function of the wavelength.

UV-visible spectra tend to show broad peaks and valleys. The spectral data that are most characteristic of a sample are as follows:

1. The wavelength(s) of maximum absorbance, called λ_{max}
2. The value of the molar absorptivity κ at each maximum

Since UV-visible spectra are broad and lacking in detail, they are rarely printed as actual spectra. The spectral information is given as a list of the value or values of λ_{max} together with the molar absorptivity for each value of λ_{max}.

The UV spectrum of isoprene (2-methyl-1,3-butadiene) is shown in Figure 12–7. This spectrum could be summarized as follows:

$$\lambda_{max} = 222 \text{ nm} \qquad \kappa = 20\,000 \text{ L/(mol·cm)}$$

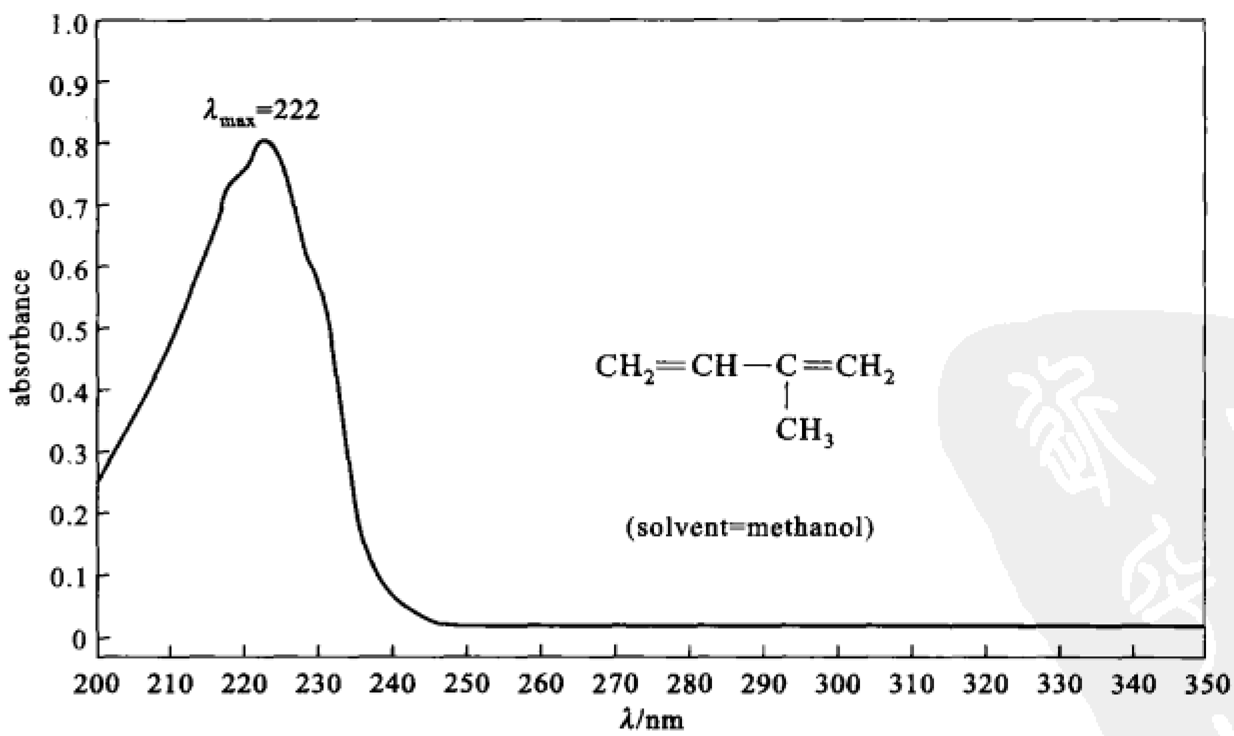


Figure 12–7 The UV spectrum of isoprene dissolved in methanol shows λ_{max} = 222 nm, κ = 20000 L/(mol·cm).

The value of λ_{max} is read directly from the spectrum, but the molar absorptivity κ must be calculated from the concentration of the solution and the path length of the cell. For an isoprene concentration of 4×10^{-5} mol/L and a 1-cm cell, the molar absorptivity is found by rearranging Beer's law ($A = \kappa c l$).

$$\kappa = \frac{A}{cl} = \frac{0.8}{4 \times 10^{-5}}\ \text{L/(mol·cm)} = 20\,000\ \text{L/(mol·cm)}$$

Molar absorptivities in the range of 5 000 to 30 000 L/(mol·cm) are typical for the $\pi \rightarrow \pi^*$ transitions of conjugated polyene systems. Such large molar absorptivities are helpful, since spectra may be obtained with very small amounts of sample. On the other hand, samples and solvents for UV spectroscopy must be extremely pure. A minute impurity with a large molar absorptivity can easily obscure the spectrum of the desired compound.

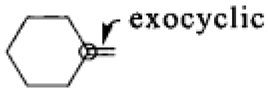
PROBLEM 12−2

One milligram of a compound of molecular weight 160 is dissolved in 10 mL of ethanol, and the solution is poured into a 1-cm UV cell. The UV spectrum is taken, and there is an absorption at λ_{max} = 247 nm. The maximum absorbance at 247 nm is 0.50. Calculate the value of κ for this absorption.

12−16 Interpreting UV-Visible Spectra

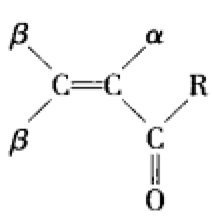
The values of λ_{max} and κ for conjugated molecules depend on the exact nature of the conjugated system and its substituents. For most purposes, however, we can use some simple generalizations for estimating approximate values of λ_{max} for common types of systems. The most useful correlations between structures and UV spectra were developed in the early 1940s by R. B. Woodward and L. F. Fieser. These correlations are called the **Woodward-Fieser rules**. The rules presented here predict only the lowest-energy $\pi \rightarrow \pi^*$ transition from the HOMO to the LUMO. Values of λ_{max} measured in different solvents can be different, so we generally assume that ethanol is the solvent. These rules are summarized in Tables 12−4 and 12−5.

TABLE 12−4 The Woodward-Fieser Rules for Conjugated Dienes: Values for Auxochromic Groups

Grouping	Substituent Correction/nm
another conjugated C═C	+30
alkyl group	+5
alkoxy (—OR) group	0
If one of the double bonds in the chromophore is exocyclic, add another 5 nm:	
	+5 (in addition to 30 nm if it lengthens the system)
exocyclic double bond(环外双键)	

Note: These values are added to the base value for the diene system.

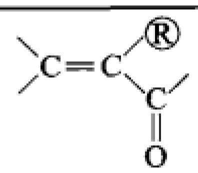
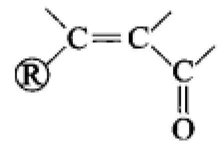
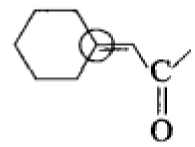
TABLE 12−5 The Woodward-Fieser Rules for Conjugated Ketones and Aldehydes



general structure

Base values: 210 nm if R = H (aldehyde)
215 nm if R = alkyl (ketone)

Continue

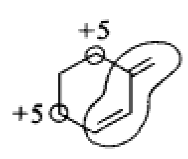
Grouping	Position	Correction
alkyl group, α		+10 nm
alkyl group, β		+12 nm
exocyclic position of a C=C bond		+5 nm
additional conjugated double bond		+30 nm

12–16A UV Spectra of Dienes and Polyenes

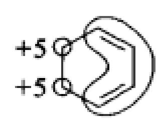
Bathochromic Effects of Alkyl Groups A molecule's system of conjugated double bonds (the chromophore) is the largest factor in determining its UV spectrum, but the absorption is also affected by alkyl substituents. Each alkyl group attached to the chromophore serves as an auxochrome, producing a small bathochromic shift of about 5 nm.

Conformation Effects For dienes that are predominantly in the *s*-trans conformation (either free to rotate or held in the *s*-trans conformation), Woodward and Fieser used a base value of 217 nm, the λ_{max} for unsubstituted 1,3-butadiene. To this value, add 5 nm for each alkyl substituent. For dienes that are held in the *s*-cis conformation by a six-membered ring, the base value is 253 nm for the diene, plus 5 nm for each alkyl substituent.

acyclic (*s*-trans) diene
base 217 nm



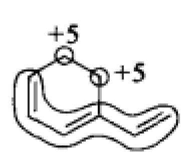
transoid cyclic diene
base 217 nm
+2 alkyl×(5 nm)



cisoid cyclic diene
base 253 nm
+2 alkyl×(5 nm)

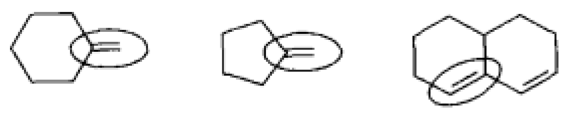
Additional Conjugated Double Bonds For trienes and larger conjugated systems, add 30 nm to the base value for each additional double bond. The additional double bond must be attached at the end of the conjugated system to extend the length of the polyene system, however, in order to have this large 30-nm contribution.

acyclic (*s*-trans) triene
217 nm+30 nm=base 247 nm



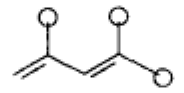
cisoid cyclic triene
253 nm+30 nm=base 283 nm
+2 alkyl×(5 nm)

Contributions of auxochromic groups are added to the base values of the polyene chromophore. Add 5 nm for each alkyl group and 5 nm if one of the double bonds in the conjugated system is exocyclic to a ring. An exocyclic double bond is one that is attached to a ring at one end.



exocyclic double bonds

Examples The best way to learn to use the rules for predicting UV absorptions is to work through some examples. The following examples show several structures that follow the rules closely and one that does not.

1. 

2,4-dimethyl-1,3-pentadiene

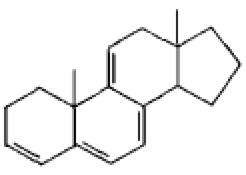
base: 217 nm
three alkyl groups: 15 nm
predicted λ_{max}: 232 nm; observed: 232 nm

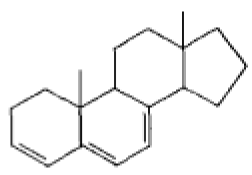
2.

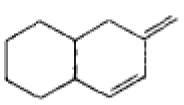
base: 217 nm
two alkyl groups: 10 nm
exocyclic C=C: 5 nm
predicted λ_{max}: 232 nm; observed: 230 nm

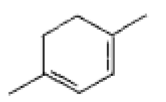
PROBLEM 12-3

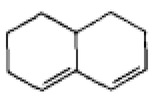
Using the examples in Section 12-16A to guide you, match the following UV absorption maxima (λ_{max}) with the corresponding compounds: (1) 232 nm; (2) 237 nm; (3) 273 nm; (4) 283 nm; (5) 313 nm; (6) 353 nm.

(a) 

(b) 

(c) 

(d) 

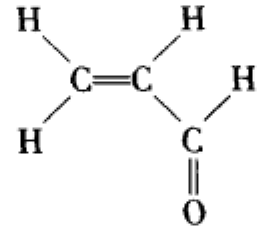
(e) 

12-16B UV Spectra of Conjugated Ketones and Aldehydes

$\pi \to \pi^*$ Transitions As with dienes and polyenes, the strongest absorptions in the UV spectra of aldehydes and ketones result from $\pi \to \pi^*$ electronic transitions. These absorptions are observable (λ_{max} > 200 nm) only if the carbonyl double bond is conjugated with another double bond.

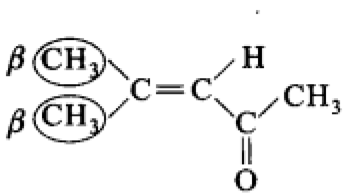
The Woodward-Fieser rules for conjugated ketones and aldehydes appear in Table 12-5. Note that bathochromic effects of alkyl groups depend on their location: 10 nm for groups α to the carbonyl and 12 nm for groups in β positions. Contributions from additional conjugated double bonds (30 nm) and exocyclic positions of double bonds (5 nm) are similar to those in dienes and polyenes.

The following examples show how the Woodward-Fieser rules predict values of λ_{max} for a variety of conjugated ketones and aldehydes. Notice that the molar absorptivities (κ) for these transitions are quite large [>5 000 L/(mol·cm)], as we also observed for $\pi \to \pi^*$ transitions in conjugated dienes and polyenes.

1. 

Base value	210 nm
(no corrections)	______
Predicted λ_{max}	210 nm

Experimental: λ_{max} = 210 nm, κ = 11 000 L/(mol·cm)

2. 

Base value	215 nm
$2 \times \beta$ substituent	24 nm
Predicted λ_{max}	239 nm

Experimental: λ_{max} = 237 nm, κ = 12 000 L/(mol·cm)

Summary in Chinese

本章概要

一、红外光谱(infrared spectroscopy)

1. 电磁波的波粒二象性:光是电磁波的一种,具有波粒二象性,频率(ν)、波长(λ)与光速(c)的基本关系式为:$\lambda\nu = c$;光量子能量为:$E = h\nu$。

2. 红外光谱区域:目前广泛使用的傅里叶变换红外光谱仪一般测试的波数范围为4 000 ~ 400 cm^{-1},属中红外区(2.5 ~ 25 μm,波数为波长的倒数)。有机化合物各种官能团的吸收都在1 600 ~ 3 700 cm^{-1},此区域称为官能团吸收区或高频区,小于1 600 cm^{-1}的区域称为指纹区或低频区。

3. 红外光谱基本原理:物质的分子及分子中的原子、电子、原子核等是运动着的,不同的质点、不同的运动状态具有不同的能量,能量差是量子化的。与产生红外光谱有关的运动方式是原子的振动和分子的转动。用红外光照射化合物分子,当光的能量恰好等于基态与某一激发态的能量之差时($\Delta E = h\nu$),分子能够吸收红外光的能量,使分子、原子的振动和转动能级发生跃迁,从而产生红外吸收光谱。分子吸收红外光的频率反映了分子内质点的种类和运动状态,因此,测定化合物的红外吸收光谱可以表征其分子结构。

4. 分子振动与吸收频率:分子中原子的振动方式主要有两种,即伸缩振动和弯曲振动。伸缩振动又分为对称伸缩振动(ν_s)和不对称伸缩振动(ν_{as}),弯曲振动又分为面内弯曲振动(δ)和面外弯曲振动(γ)。振动频率与振动的两原子的相对原子质量和振动键的力常数(κ)有关,振动原子的相对原子质量越小,振动频率越高;振动键的键能越大,力常数越大,振动频率越高。只有能引起分子偶极矩变化的振动才能吸收与其振动频率一致的红外光,产生红外吸收光谱。不能引起分子偶极矩变化的振动为红外非活性的。

5. 有机化合物中主要基团的红外光谱特征吸收峰:

官能团	波数/cm^{-1}	说　明
醇、羧酸 O—H	3 600 ~ 3 650(游离的) 3 300 ~ 3 500(缔合的)	宽峰
胺、酰胺 N—H	3 200 ~ 3 500	宽峰、尖峰或多重宽峰
端炔烃 ≡C—H	3 300	尖峰,较强
烯烃 =C(H)—	3 000 ~ 3 100	
烷烃 —C(—)(—)—H	2 800 ~ 3 000	
炔烃 —C≡C—	2 100 ~ 2 250	一般低于 2 200 cm^{-1}
腈 —C≡N	2 200 ~ 2 260	高于 2 200 cm^{-1}
醛、酮 >C=O	1 680 ~ 1 750	共轭体系可使波数降低,醛在 2 700 ~ 2 800 cm^{-1} 有醛基C—H 伸缩振动吸收峰
羧酸 >C=O	1 710 ~ 1 720	共轭体系可使波数降低,应有 O—H 伸缩振动吸收峰

续表

官能团	波数/cm^{-1}	说　　明
酯 >C=O	1735 ~ 1750	共轭体系可使波数降低
酰胺 >C=O	1630 ~ 1690	共轭体系可使波数降低，应有 N—H 伸缩振动吸收峰
烯烃 >C=C<	1600 ~ 1680	共轭体系可使波数降低
亚胺 >C=N—	1640 ~ 1690	一般比C=C 吸收峰强
醚、酯、醇 C—O	1000 ~ 1200	

6. 红外光谱的应用：鉴定化合物的官能团；通过与已知化合物的标准谱图比对，推断分子结构；结合其他结构测试方法，推断未知化合物的结构。

二、紫外光谱（ultraviolet spectroscopy）

1. 朗伯－比尔（Lambert-Beer）定律

$$A = \lg\left(\frac{I_r}{I_s}\right) = \kappa cl$$

式中：A 为吸光度；I_r 为入射光强度；I_s 为透射光强度；c 为样品溶液的浓度，mol/L；l 为样品池长度，cm；κ 为样品的摩尔吸收系数，L/(mol·cm)，是化合物吸收光谱的特定常数。

2. 紫外－可见光谱区域：目前使用的紫外光谱仪多数将紫外和可见光谱连在一起，称为紫外－可见光谱，范围是 200 ~ 800 nm。许多有机化合物在近紫外区（200 ~ 400 nm）有特征吸收，共轭分子的吸收可出现在可见光区（400 ~ 800 nm）。化合物在紫外－可见光谱中的吸收带的位置和强度能够提供有用的分子结构信息。

3. 紫外－可见光谱基本原理：有机分子的最高占据分子轨道（HOMO）中的一个电子在吸收适当波长的光之后，跃迁到最低未占分子轨道（LUMO），形成激发态分子，产生紫外－可见吸收光谱，又称电子光谱。

4. 电子跃迁与吸收带的波长：电子跃迁主要有 $\sigma\rightarrow\sigma^*$、$n\rightarrow\sigma^*$、$n\rightarrow\pi^*$、$\pi\rightarrow\pi^*$ 四种类型，其中 $\pi\rightarrow\pi^*$ 跃迁是紫外光谱中最常见、最重要的电子跃迁形式，通常表现为强吸收带。孤立碳碳双键电子的 $\pi\rightarrow\pi^*$ 跃迁吸收光在远紫外区（100 ~ 200 nm），随着共轭体系的增大，吸收带向长波移动（红移），出现在近紫外区甚至可见光区；共轭链端位碳上烷基的增加也会使 $\pi\rightarrow\pi^*$ 吸收带发生红移。

5. 伍德瓦德－菲希（Woodward-Fieser）规则：伍德瓦德－菲希规则是根据大量共轭有机化合物的紫外－可见光谱数据总结出来的经验公式，用来估算共轭烯烃和共轭羰基化合物的 λ_{max} 值。主要考虑共轭烯烃单键－顺式/单键－反式（*s*-cis/*s*-trans）构象的影响，增加共轭双键的影响，环外双键的影响和共轭链上烷基取代基的影响。

6. 紫外－可见光谱的应用：紫外－可见光谱主要反映共轭化合物的结构特征，除此之外，还可利用紫外－可见光谱研究反应平衡，测定有机化合物 pK_a 等。

Essential Problem-Solving Skills in Chapter 12

1. Given an IR spectrum, identify the reliable characteristic peaks.

2. Explain why some characteristic peaks are usually strong or weak and why some may be absent.

3. Predict the stretching frequencies of common functional groups.

4. Identify functional groups from IR spectra.
5. Identify conjugated and strained C=O bonds and conjugated and aromatic C=C bonds from their absorptions in the IR spectrum.
6. Use values of λ_{max} from UV-visible spectra to estimate the length of conjugated systems, and compare compounds with similar structures.

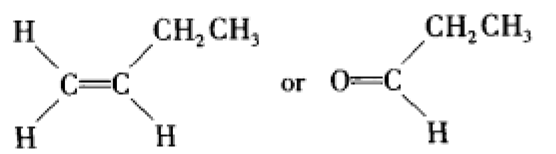
Study Problems

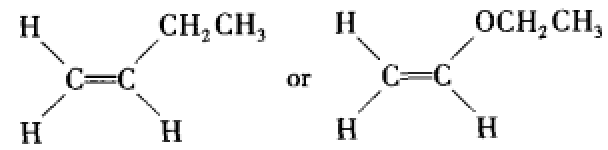
12–4 Define and give an example of each term.

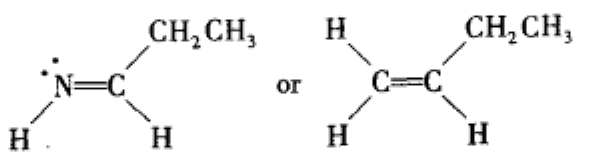
(a) fingerprint region（指纹区）
(b) an IR-active vibration（红外活性振动）
(c) an IR-inactive vibration（红外非活性振动）
(d) wavelength（波长）
(e) conjugated double bonds（共轭双键）
(f) wavenumber（波数）

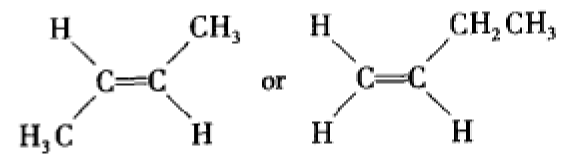
12–5 All of the following compounds absorb infrared radiation between 1 600 and 1 800 cm^{-1}. In each case,

1. Show which bonds absorb in this region.
2. Predict the approximate absorption frequencies.
3. Predict which compound of each pair absorbs more strongly in this region.

(a) 

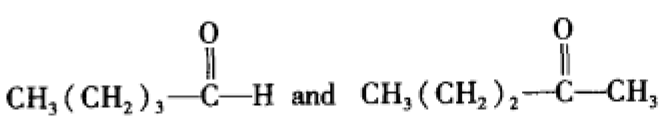
(b) 

(c) 

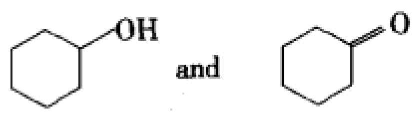
(d) 

12–6 Describe the characteristic infrared absorption frequencies that would allow you to distinguish between the following pairs of compounds.

(a) 2,3-dimethyl-2-butene and 2,3-dimethyl-1-butene
(b) cyclohexa-1,3-diene and cyclohexa-1,4-diene

(c) 

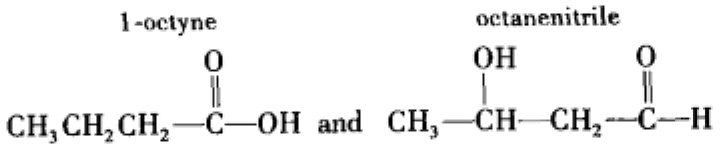
pentanal 2-pentanone

(d) 

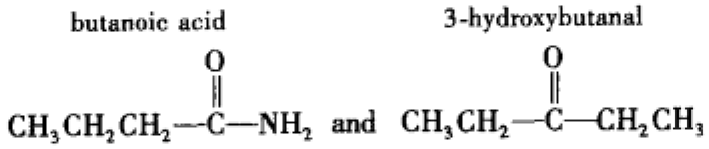
cyclohexanol cyclohexanone

(e) $CH_3(CH_2)_5$—C≡C—H and $CH_3(CH_2)_6$—C≡N

1-octyne octanenitrile

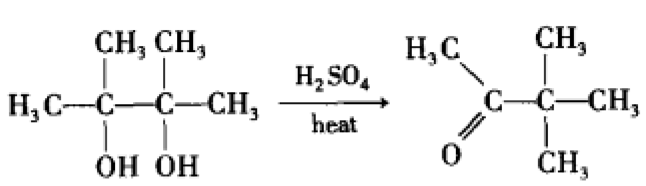
(f) 

butanoic acid 3-hydroxybutanal

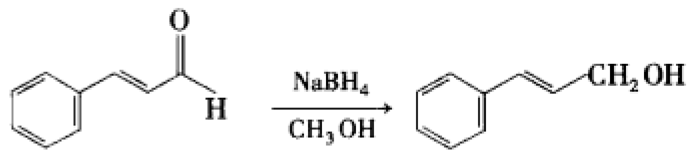
(g) 

butanamide 3-pentanone

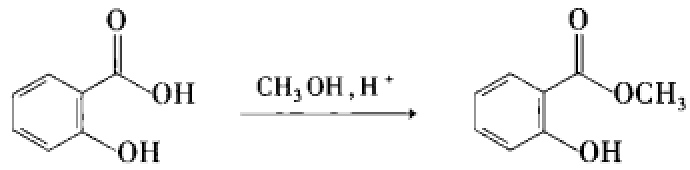
12–7 Three common lab experiments are shown. In each case, describe how the IR spectrum of the product would differ from that of the reactant. Give approximate frequencies for distinctive peaks in the IR spectrum of the reactant and also that of the product.



pinacol pinacolone

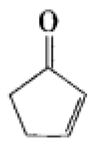


cinnamaldehyde(肉桂醛)　　cinnamyl alcohol(肉桂醇)

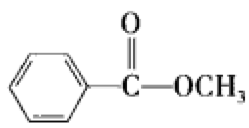


salicylic acid(水杨酸)　　methyl salicylate (wintergreen,水杨酸甲酯,冬青)

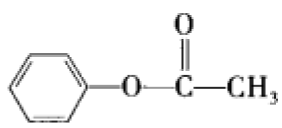
12−8 Three IR spectra are shown, corresponding to three of the following compounds. For each spectrum, determine the structure and explain how the peaks in the spectrum correspond to the structure you have chosen.



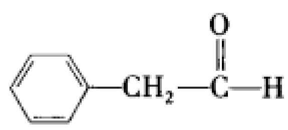
A



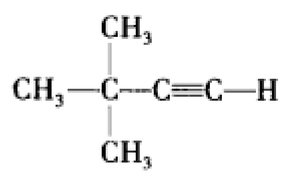
B



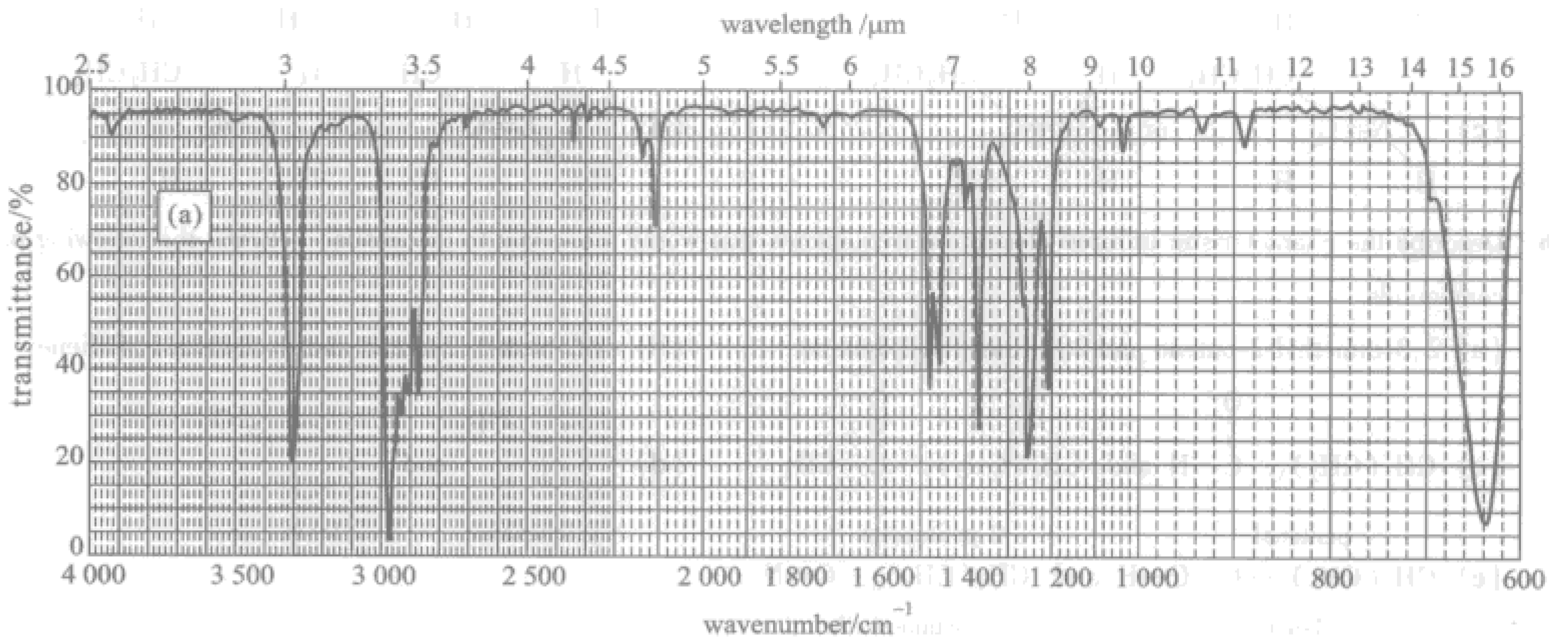
C

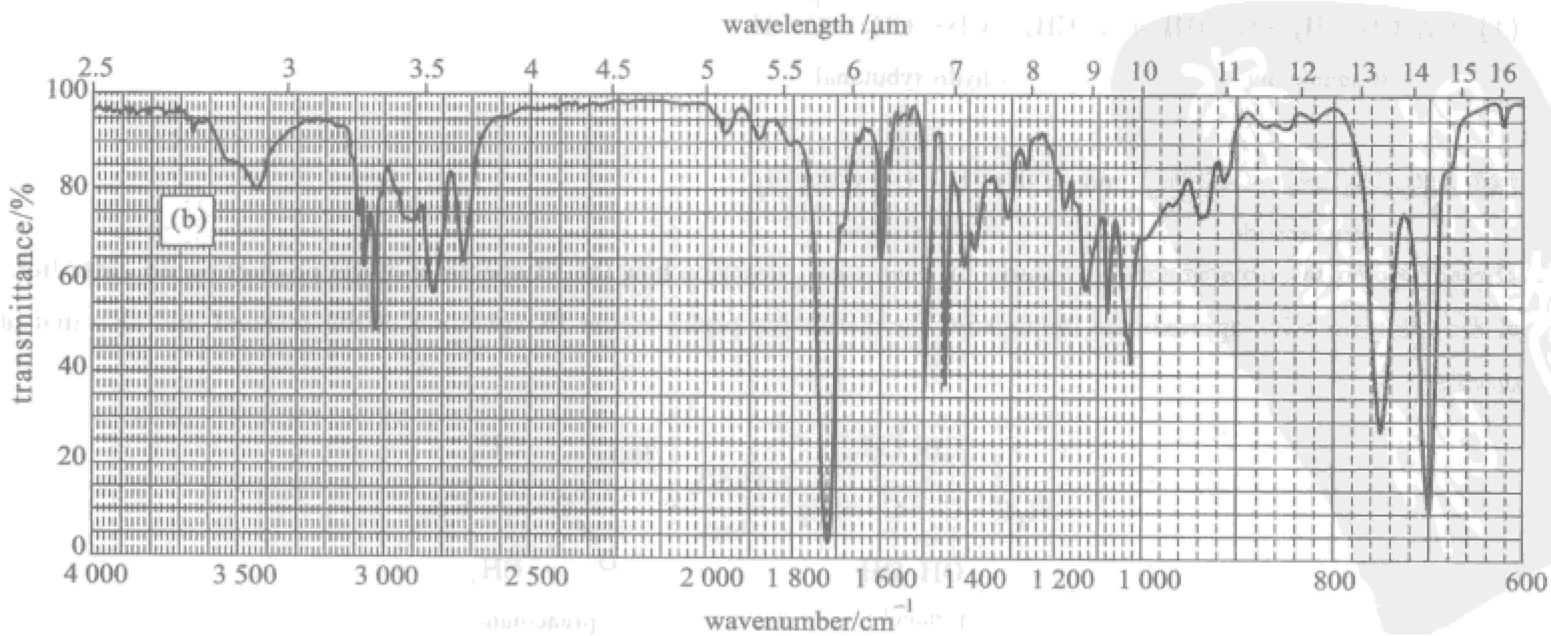


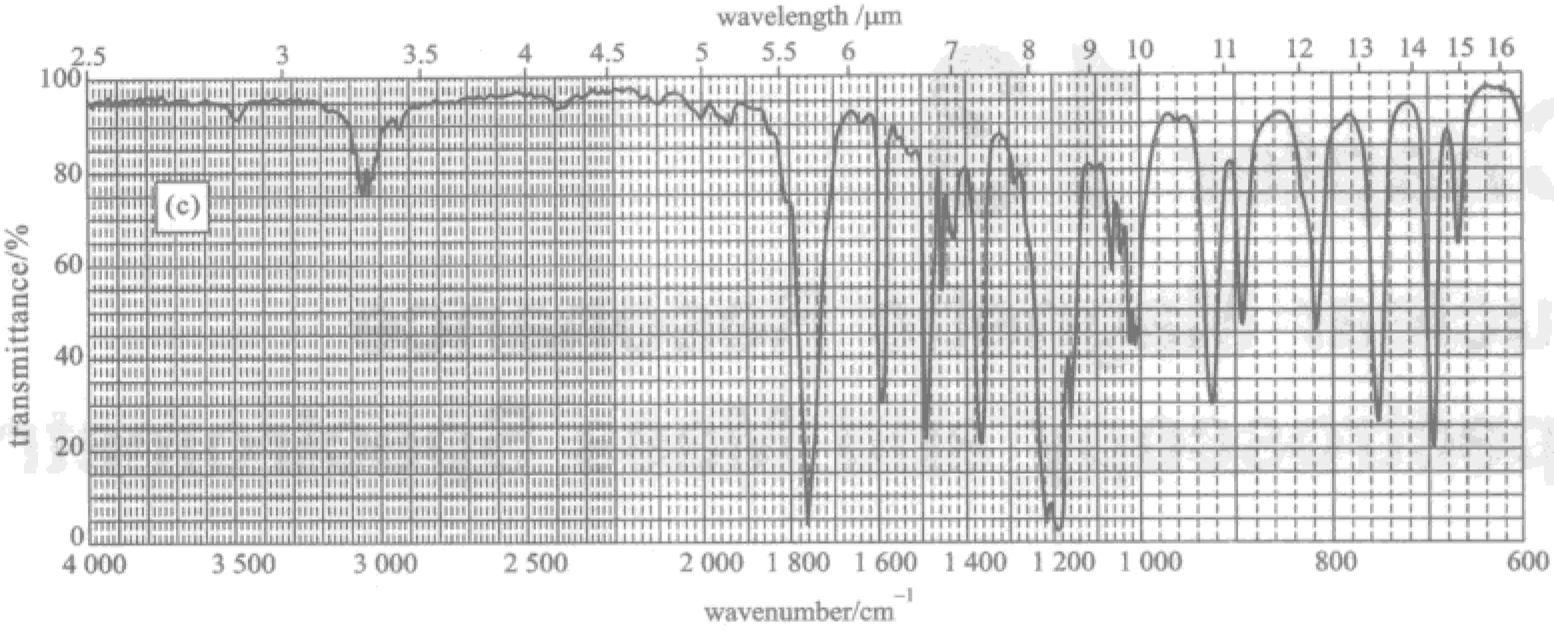
D



E



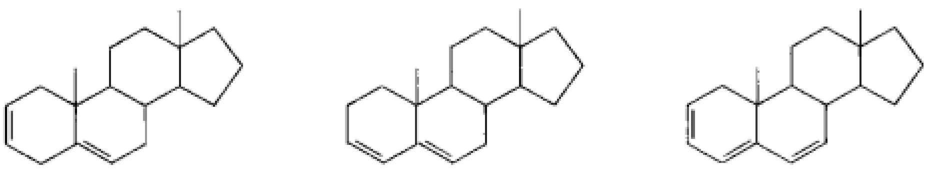




12−9 A solution was prepared using 0.0010 g of an unknown steroid (of molecular weight around 255) in 100 mL of ethanol. Some of this solution was placed in a 1-cm cell, and the UV spectrum was measured. This solution was found to have λ_{max} = 235 nm, with $A = 0.74$.

(a) Compute the value of the molar absorptivity at 235 nm.

(b) Which of the following compounds might give this spectrum?



Chapter 13

Nuclear Magnetic Resonance Spectroscopy and Mass Spectrometry

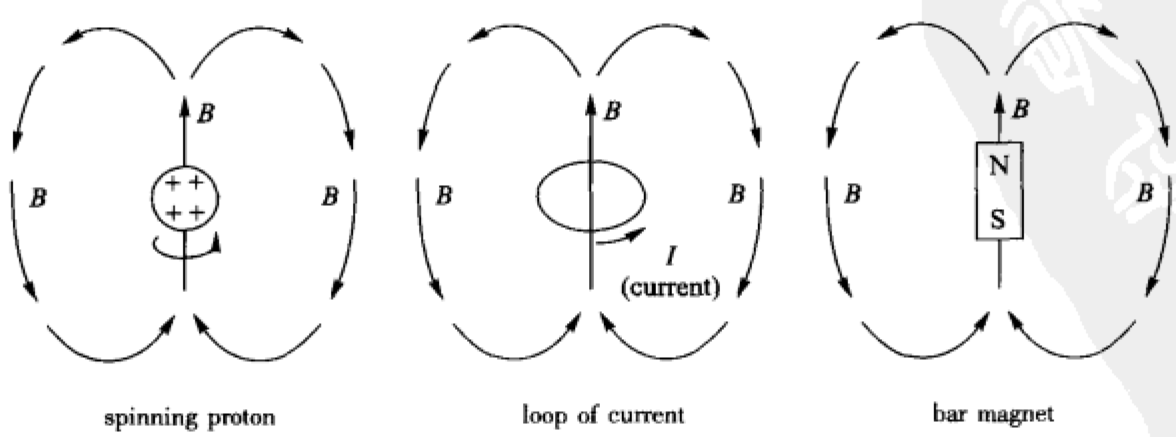
13−1 Introduction to Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance spectroscopy (**NMR**) is the most powerful tool available for organic structure determination. Like IR spectroscopy, NMR can be used with a very small sample, and it does not harm the sample. The NMR spectrum provides a great deal of information about the structure of the compound, and some structures can be determined using only the NMR spectrum. More commonly, however, the NMR spectrum is used in conjunction with other forms of spectroscopy and chemical analysis to determine the structures of complicated organic molecules.

NMR is used to study a wide variety of nuclei, including ^{1}H, ^{13}C, ^{15}N, ^{19}F, and ^{31}P. Organic chemists find **proton** (^{1}**H**) and **carbon−13** (^{13}**C**) **NMR** to be most useful because hydrogen and carbon are major components of organic compounds.

13−2 Theory of Nuclear Magnetic Resonance

A nucleus with an odd atomic number or an odd mass number has a *nuclear spin* that can be observed by the NMR spectrometer. A proton is the simplest nucleus, and its odd atomic number of 1 implies it has a spin. We can visualize a spinning proton as a rotating sphere of positive charge (Figure 13−1). This movement of charge is like an electric current in a loop of wire. It generates a magnetic field (symbolized by B) ,called the **magnetic moment**, that looks like the field of a small bar magnet.



spinning proton　　loop of current　　bar magnet

Figure 13−1 The magnetic moment. A spinning proton generates a magnetic field, called its magnetic moment. This magnetic field (B) resembles that of a small loop of current or bar magnet.

When a small bar magnet is placed in the field of a larger magnet, it twists to align itself with the field of the larger magnet—a lower energy arrangement than an orientation against the field. The same effect is seen when a proton is placed in an external magnetic field (B_0). Quantum mechanics requires the proton's magnetic moment to be aligned either *with* the external field or *against* the field. The lower-energy state with the proton aligned with the field is called the *alpha-spin* (α-spin) *state*. The higher-energy state with the proton aligned against the external magnetic field is called the *beta-spin* (β-spin) *state* (Figure 13-2).

In the absence of an external magnetic field, proton magnetic moments have random orientations. When an external magnetic field is applied, each proton in a sample assumes the α state or the β state. Because the α-spin state is lower in energy, there are more α spins than β spins.

In a strong magnetic field, the energy difference between the two spin states is larger than it is in a weaker field. In fact, the energy difference is proportional to the strength of the magnetic field, as expressed in the equation

$$\Delta E = h\nu = \gamma \frac{h}{2\pi} B_0$$

where

ΔE = energy difference between α and β states

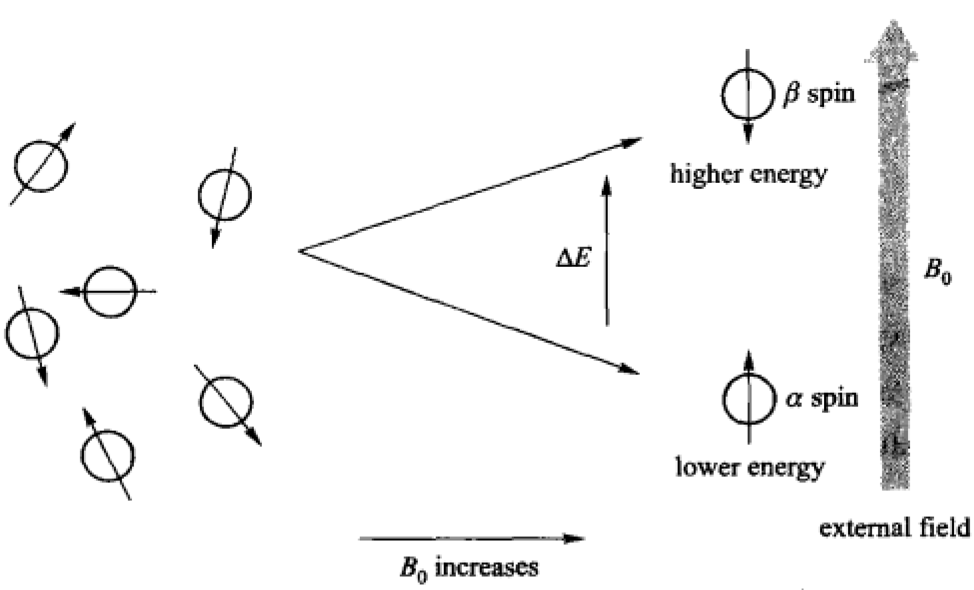
h = Planck's constant

ν = the frequency of the electromagnetic wave

B_0 = strength of the external magnetic field

γ = gyromagnetic ratio, 26 753 $(\text{s}\cdot\text{Gs})^{-1}$ for a proton

When a nucleus is subjected to the right combination of magnetic field and electromagnetic radiation to flip its spin, it is said to be "in resonance" (Figure 13-3), and its absorption of energy is detected by the NMR spectrometer. This is the origin of the term "nuclear magnetic resonance."



No Field
spins in all directions
no energy difference

Magnetic Field
spins aligned with
or against field

Figure 13-2 Spin states of the proton.

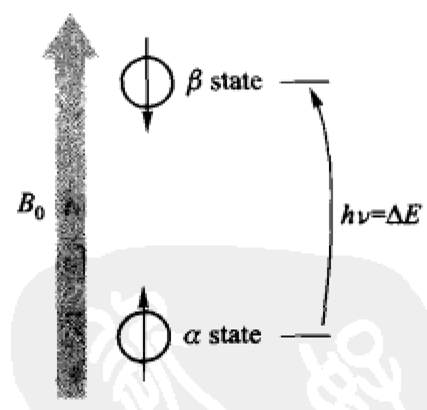


Figure 13-3 NMR absorption. A nucleus is "in resonance" when it is irradiated with radio-frequency photons having energy equal to the energy difference between the spin states. Under these conditions, a proton in the α-spin state can absorb a photon and flip to the β-spin state.

Rearranging to solve for ν shows that the resonance frequency ν is proportional to the applied magnetic field (B_0) and the gyromagnetic ratio (γ):

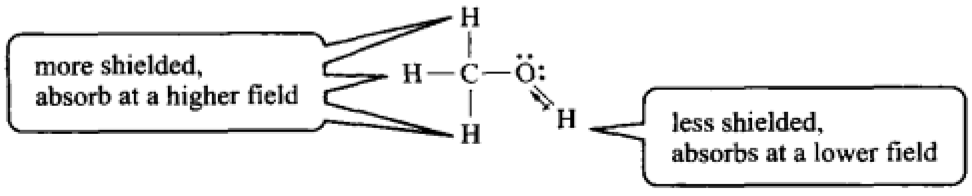
$$\nu = \frac{1}{2\pi}\gamma B_0$$

13-3 Magnetic Shielding by Electrons

Up to now, we have considered the resonance of a naked proton in a magnetic field, but real protons in organic compounds are not naked. They are surrounded by electrons that partially shield them from the external magnetic field. The electrons circulate and generate a small **induced magnetic field** that opposes the externally applied field.

In a molecule, the electron cloud around each nucleus acts like a loop of wire, rotating in response to the external field. This induced rotation is a circular current whose magnetic field opposes the external field. The result is that the magnetic field at the nucleus is weaker than the external field , and we say the nucleus is **shielded**. The effective magnetic field *at the shielded proton* is always weaker than the external field, so the applied field must be increased for resonance to occur at a given frequency.

If all protons were shielded by the same amount, they would all be in resonance at the same combination of frequency and magnetic field. Fortunately, protons in different chemical environments are shielded by different amounts. In methanol, for example, the electronegative oxygen atom withdraws some electron density from around the hydroxyl proton. The hydroxyl proton is not shielded as much as the methyl protons, so the hydroxyl proton absorbs at a lower field than the methyl protons (but still at a higher field than a naked proton). We say that the hydroxyl proton is **deshielded** somewhat by the presence of the electronegative oxygen atom.



Because of the diverse and complex structures of organic molecules, the shielding effects of electrons at various positions are generally different. A careful measurement of the field strengths required for resonance of the various protons in a molecule provides us with two important types of information:

1. The *number of different absorptions* (also called *signals* or *peaks*) implies how many different types of protons are present.

2. The *amount of shielding* shown by these absorptions often implies the electronic structure of the molecule close to each type of proton.

Two other aspects of the NMR spectrum we will consider are the intensities of the signals and their splitting patterns:

3. The *intensities of the signals* imply how many protons of each type are present.

4. The *splitting of the signals* gives information about other nearby protons.

Before discussing the design of spectrometers, let's review what happens in an NMR spectrometer. Protons (in the sample compound) are placed in a magnetic field, where they align either with the field or against it.

While still in the magnetic field, the protons are subjected to radiation of a frequency they can absorb by changing their orientation relative to the field. If protons were isolated, they would all absorb at the same frequency, proportional to the magnetic field.

But protons in a molecule are partially shielded from the magnetic field, and this shielding depends on each proton's environment. Thus, protons in different environments within a molecule exposed to a constant frequency absorb the radiation at different magnetic field strengths. The NMR spectrometer must be equipped to vary the magnetic field and plot a graph of energy absorption as a function of the magnetic field strength. Such a graph is called a **nuclear magnetic resonance spectrum.**

13－4 The NMR Spectrometer

The simplest type of NMR spectrometer (Figure 13－4) consists of four parts:

1. A stable magnet, with a sensitive controller to produce a precise magnetic field
2. A radio-frequency (RF) transmitter, emitting a precise frequency
3. A detector to measure the sample's absorption of RF energy
4. A recorder to plot the output from the detector versus the applied magnetic field

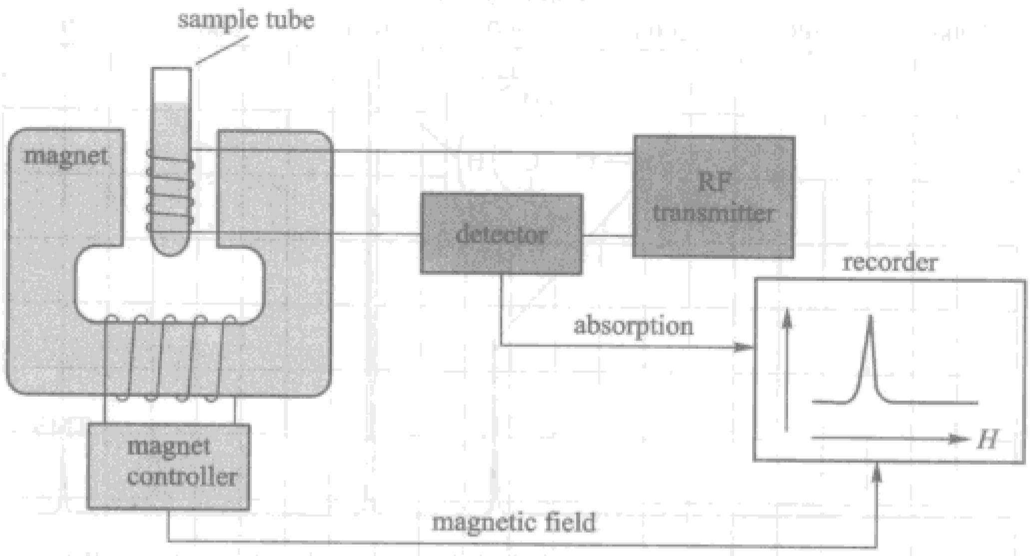


Figure 13－4 Simplified block diagram of a nuclear magnetic resonance spectrometer.

The recorder prints a graph of absorption (on the y axis) as a function of the applied magnetic field (on the x axis). Higher values of the magnetic field are toward the right (**upfield**), and lower values are toward the left (**downfield**). The absorptions of more shielded protons appear upfield, toward the right of the spectrum, and less shielded protons appear downfield, toward the left.

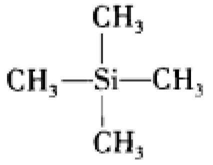
13－5 The Chemical Shift

13－5A Measurement of Chemical Shifts

The variations in the positions of NMR absorptions, arisng from electronic shielding and deshielding, are called **chemical shifts.**

Chemical shift The difference (in parts per million) between the resonance frequency of the proton being observed and that of tetramethylsilane (TMS).

Chemical shifts are measured in *parts per million*, a dimensionless fraction of the total applied field. The horizontal axis of the NMR spectrum is calibrated in hertz. The most common scale of chemical shifts is the δ (delta) scale. The signal from tetramethylsilane (TMS) is *defined* as 0.00 on the δ scale. Most protons absorb at lower fields than TMS, so the δ scale increases toward lower field (toward the left of the spectrum).



tetramethylsilane (TMS, 四甲基硅)
a reference compound

A chemical shift can be calculated by dividing the shift measured in hertz by the spectrometer frequency measured in millions of hertz (megahertz, or MHz).

$$\text{chemical shift} = \frac{\text{shift downfield from TMS (Hz)}}{\text{total spectrometer frequency (MHz)}} \times 10^6$$

The chemical shift of a given proton is the same regardless of the operating field and frequency of the spectrometer. The use of chemical shifts to describe absorptions standardizes values for all NMR spectrometers.

The 300-MHz NMR spectrum of methanol (Figure 13−5) shows the two signals from methanol together with the TMS reference peak at δ0.0. The methyl protons absorb 1025 Hz downfield from TMS. Their chemical shift is 3.4, so we say that the methyl protons absorb at δ3.4. The hydroxyl proton absorbs farther downfield, at a position around 1450 Hz from TMS. Its chemical shift is δ4.8.

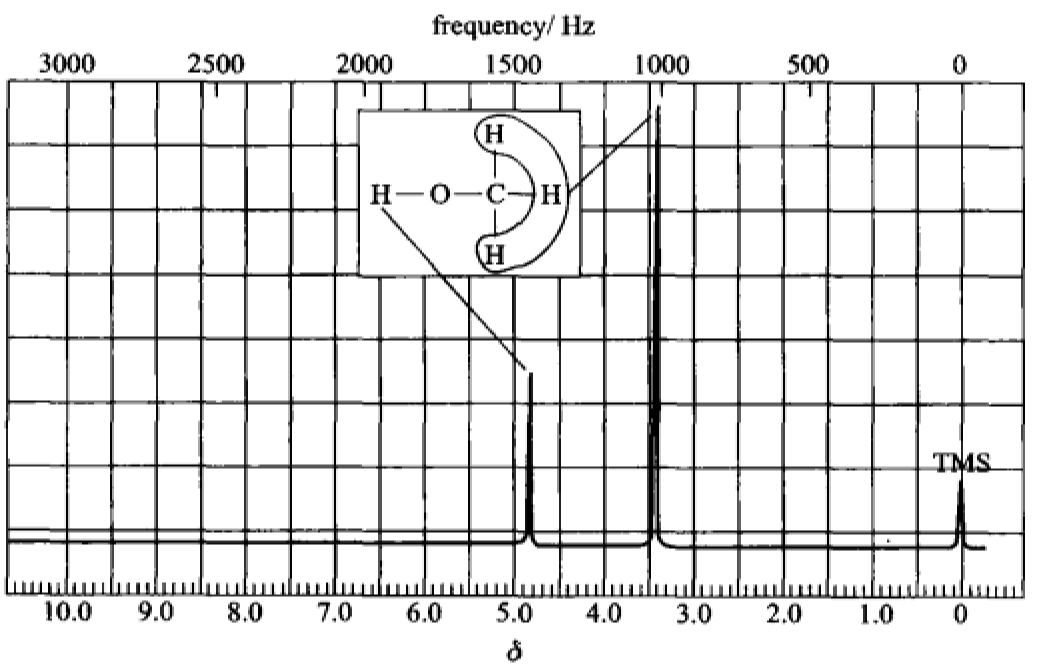


Figure 13−5 A 300-MHz proton NMR spectrum of methanol. The methyl protons absorb at δ3.4, and the hydroxyl proton absorbs at δ4.8.

Both the hydroxyl proton and the methyl protons of methanol show the deshielding effects of the electronegative oxygen atom. The chemical shift of a methyl group in an alkane is about δ0.9. Therefore, the methanol oxygen deshields the methyl protons by an additional 2.5. Other electronegative atoms produce similar deshielding effects. Table 13−1 compares the chemical shifts of methanol with those of the methyl halides. Notice that the chemical shift of the methyl protons depends on the electronegativity of the substituent, with more electronegative substituents deshielding more and giving larger chemical shifts.

TABLE 13−1 Variation of Chemical Shift with Electronegativity

	X in CH_3—X				
	F	OH	Cl	Br	I
electronegativity of X	4.0	3.4	3.2	3.0	2.7
chemical shift of CH_3—X	δ4.3	δ3.4	δ3.0	δ2.7	δ2.2

The effect of an electronegative group on the chemical shift also depends on its distance from the protons. In methanol, the hydroxyl proton is separated from oxygen by one bond, and its chemical shift is δ4.8. The methyl protons are separated from oxygen by two bonds, and their chemical shift is δ3.4. In general, the effect of an electron-withdrawing substituent decreases with increasing distance, and the effects are usually negligible on protons that are separated from the electronegative group by four or more bonds.

13−5B Characteristic Values of Chemical Shifts

Since the chemical shift of a proton is determined by its environment, we can construct a table of approximate chemical shifts for many types of compounds. Let's begin with a short table of representative chemical shifts (Table 13−2) and consider the reasons for some of the more interesting and unusual values.

TABLE 13−2 Typical values of Chemical Shifts

Type of Proton	Approximate δ	Type of Proton	Approximate δ
alkane($—CH_3$)	0.9	$>C=C<$ (CH_3)	1.7
alkane($—CH_2—$)	1.3		
alkane($—\overset{\mid}{C}H—$)	1.4	Ph—H	7.2
		Ph—CH_3	2.3
$—\overset{O}{\overset{\Vert}{C}}—CH_3$	2.1	R—CHO	9—10
$—C\equiv C—H$	2.5	R—COOH	10—12
R—CH_2—X	3—4	R—OH	variable, about 2—5
(X = halogen, O)		Ar—OH	variable, about 4—7
$>C=C<$ (H)	5—6	R—NH_2	variable, about 1.5—4

Note: These values are approximate, as all chemical shifts are affected by neighboring substituents. The numbers given here assume that alkyl groups are the only other substituents present.

Vinyl and Aromatic Protons Table 13−2 shows that double bonds and aromatic rings produce large deshielding effects on their vinyl and aromatic protons. These deshielding effects result from the same type of circulation of electrons that normally shields nuclei from the magnetic field. In benzene and its derivatives, the aromatic ring of pi bonding electrons acts as a conductor, and the external magnetic field induces a *ring current* (Figure 13−6). At the center of the ring, the induced field acts to oppose the external field. These induced field lines curve around. however, and on the edge of the ring the induced field *adds to* the external field. As a result, the aromatic protons are actually *deshielded*, resulting in absorption at low values of the applied magnetic field. Benzene absorbs at δ7.2, and most aromatic protons absorb in the range of δ7 to δ8.

We should remember that the benzene molecule is not always lined up in the position shown in Figure 13−6. Because benzene is constantly tumbling in the solution, the chemical shift observed for its protons is an average of all the possible orientations. If we could hold a benzene molecule in the position shown in Figure 13−6, its protons would absorb at a field even lower than δ7.2. Other orientations, such as the one with the benzene ring edge-on to the magnetic field, would be less deshielded and would absorb at a higher field. It is the *average* of all these orientations that is observed by the resonance at δ7.2.

The pi electrons of an alkene deshield the vinyl protons in the same way that an aromatic ring of electrons deshields the aromatic protons. The effect is not as large in the alkene, however, because there is not such a

large, effective ring of electrons as there is in benzene. Most vinyl protons absorb in the range of δ5 to δ6.

Acetylenic Hydrogens Since the pi bond of an alkene deshields the vinyl protons, we might expect an acetylenic hydrogen (—C≡C—H) to be even more deshielded by the two pi bonds of the triple bond. The opposite is true: Acetylenic hydrogens absorb around δ2.5, compared with δ5 to δ6 for vinyl protons. Figure 13-7 shows that the triple bond has a cylinder of electron density surrounding the sigma bond. As the molecules tumble in solution, in some orientations this cylinder of electrons can circulate to produce an induced magnetic field. The acetylenic proton lies along the *axis* of this induced field, which is a shielded region. When this shielded orientation is averaged with all other possible orientations, the result is a resonance around δ2.5.

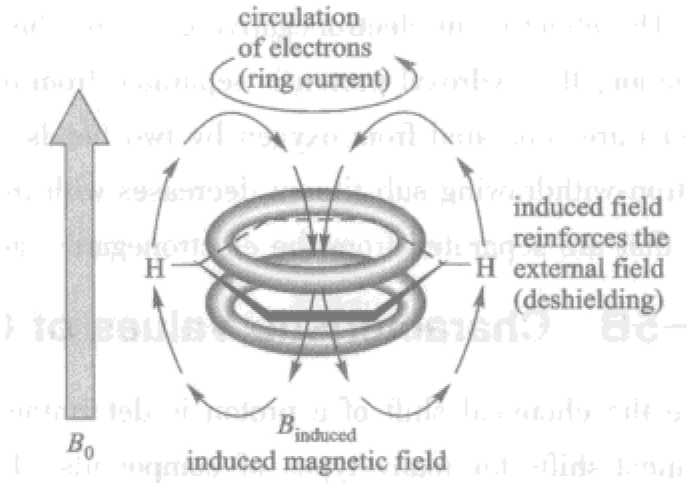


Figure 13-6 Aromatic ring current. The induced magnetic field of the circulating aromatic electrons opposes the applied magnetic field along the axis of the ring. The aromatic hydrogens are on the equator of the ring, where the induced field lines curve around and reinforce the applied field.

Aldehyde Protons Aldehyde protons (—CHO) absorb at even lower fields than vinyl protons and aromatic protons: between δ9 and δ10. Figure 13-8 shows that the aldehyde proton is deshielded both by the circulation of the electrons in the double bond and by the inductive electron-withdrawing effect of the carbonyl oxygen atom.

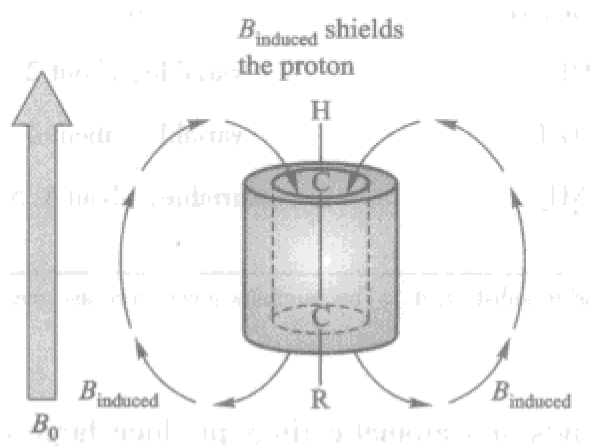


Figure 13-7 Partial shielding by a triple bond. When the acetylenic triple bond is aligned with the magnetic field, the cylinder of electrons circulates to create an induced magnetic field. The acetylenic proton lies along the axis of this field, which opposes the external field.

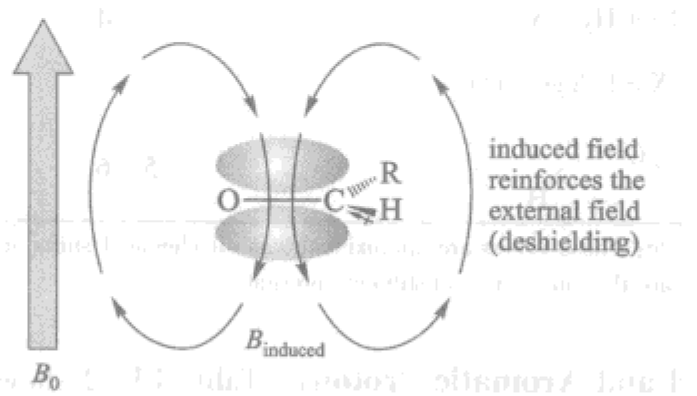
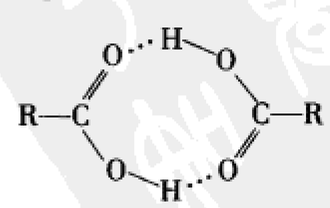


Figure 13-8 Deshielding of the aldehyde proton. Like a vinyl proton, the aldehyde proton is deshielded by the circulation of electrons in the pi bond. It is also deshielded by the electron-withdrawing effect of the carbonyl (C=O) group, giving a resonance between δ9 and δ10.

Hydrogen-Bonded Protons The chemical shifts of O—H protons in alcohols and N—H protons in amines depend on the concentration. In concentrated solutions, these protons are deshielded by hydrogen bonding, and they absorb at a relatively low field: about δ3.5 for an amine N—H and about δ4.5 for an alcohol O—H. When the alcohol or amine is diluted with a non-hydrogen-bonding solvent such as CCl_4, hydrogen bonding becomes less important. In dilute solutions, these signals are observed around δ2.



carboxylic acid dimer
(羧酸二聚物)

Hydrogen bonding and the proton exchange that accompanies it may contribute to

a broadening of the peak from an O—H or N—H proton. A broad peak appears because protons exchange from one molecule to another during the NMR resonance (see Section 13-9). The protons pass through a variety of environments during this exchange, absorbing over a wider range of frequencies and field strengths.

Carboxylic Acid Protons Because carboxylic acid protons are bonded to an oxygen next to a carbonyl group, they have considerable positive character. They are strongly deshielded and absorb at chemical shifts greater than δ10. Carboxylic acids frequently exist as hydrogen-bonded dimers, with moderate rates of proton exchange that broaden the absorption of the acid proton.

13-6 The Number of Signals

In general, the number of NMR signals corresponds to the number of different kinds of protons present in the molecule. Protons in identical chemical environments with the same shielding have the same chemical shift. Such protons are said to be **chemically equivalent.** This is what is meant whenever we use the term *equivalent* in discussing NMR spectroscopy.

The spectrum of *t*-butyl acetoacetate (Figure 13-9) shows three types of protons: the *t*-butyl protons (*a*), with a chemical shift of δ1.5; the methyl protons (*b*), deshielded by an adjacent carbonyl group, with a chemical shift of δ2.25; and the methylene protons (*c*), deshielded by two adjacent carbonyl groups, at δ3.35.

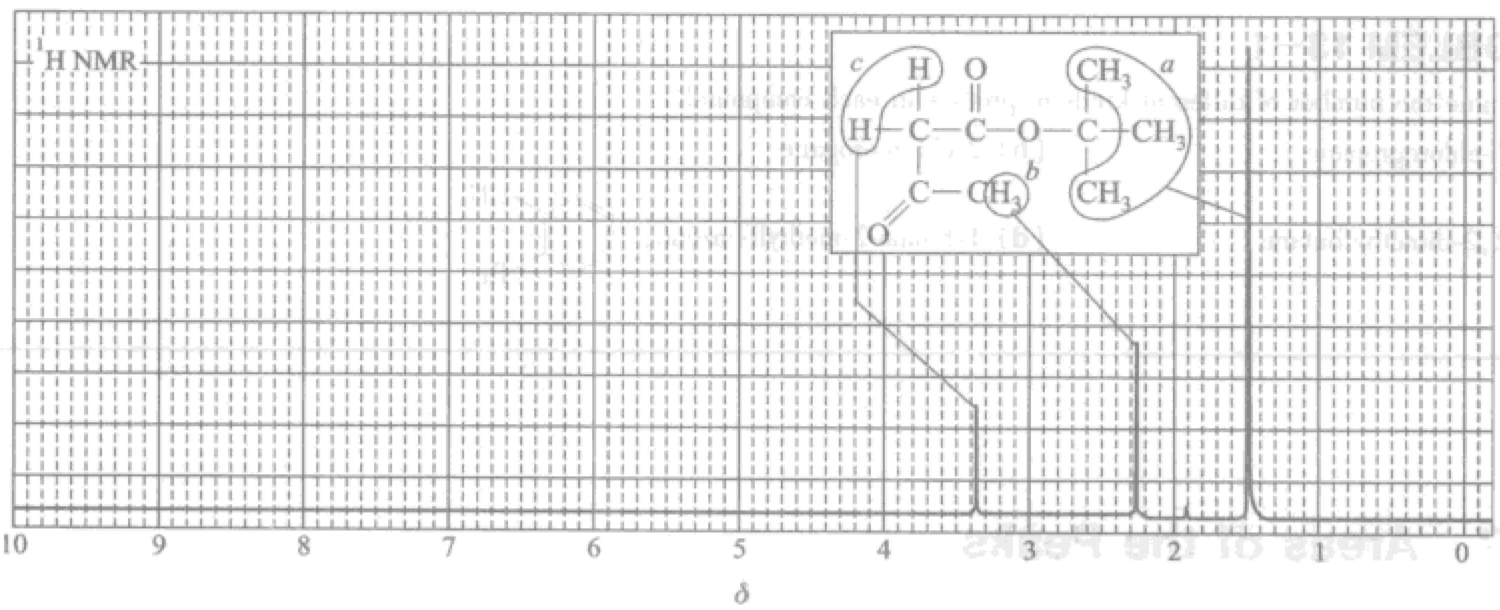


Figure 13-9 *t*-Butyl acetoacetate has three types of protons, giving three signals in the NMR spectrum.

In some cases, there may be fewer signals in the NMR spectrum than there are different types of protons in the molecule. For example, Figure 13-10 shows the structure and spectrum of *o*-xylene (1,2-dimethylbenzene). There are three different types of protons, labeled *a* for the two equivalent methyl groups, *b* for the protons adjacent to the methyl groups, and *c* for the protons two carbons removed. The spectrum shows only two distinct signals, however.

The upfield signal at δ2.3 corresponds to the six methyl protons, H^a. The absorption at δ7.2 corresponds to all four of the aromatic protons, H^b and H^c. Although the two types of aromatic protons are different, the methyl groups do not strongly influence the electron density of the ring or the amount of shielding felt by any of the substituents on the ring. The aromatic protons produce two signals, but these signals happen to occur at nearly the same chemical shift. Protons that are not chemically equivalent but happen to absorb at the same chemical shift are said to be **accidentally equivalent.**

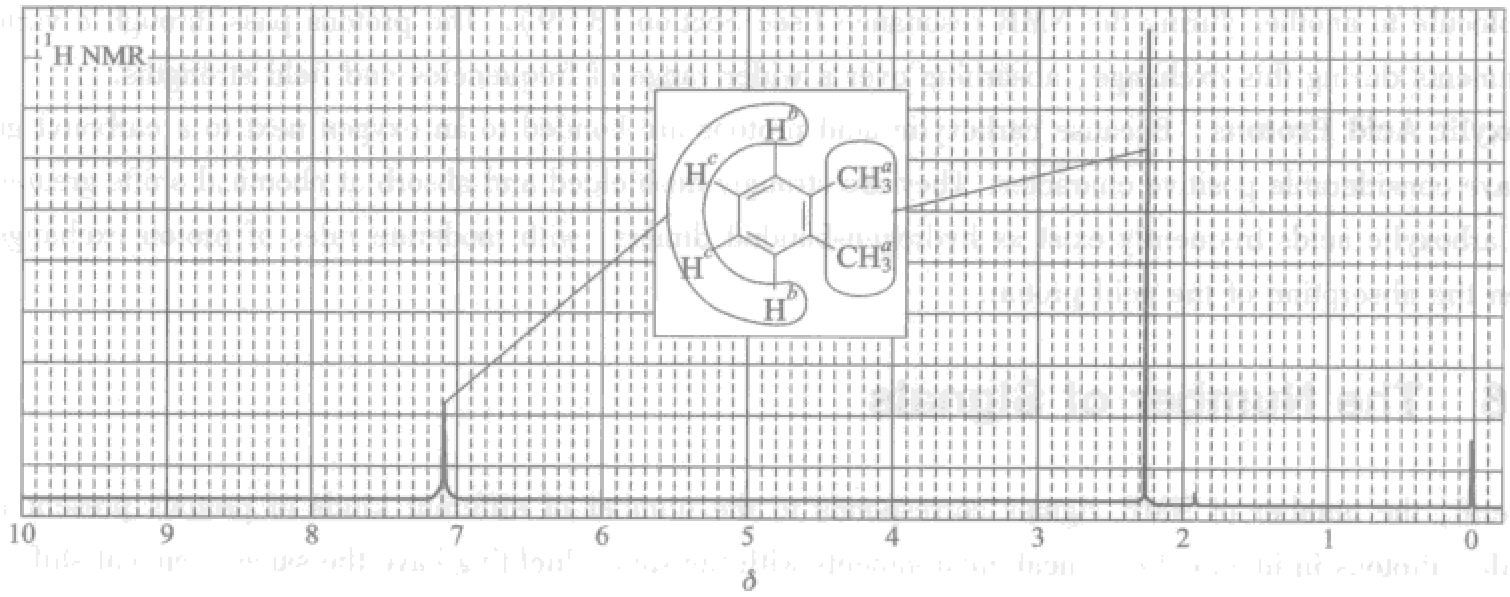


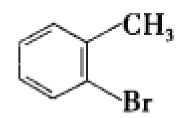
Figure 13-10 Proton NMR spectrum of *o*-xylene. There are three types of protons in *o*-xylene, but only two absorptions are seen in the spectrum. The aromatic protons H^b and H^c are accidentally equivalent, producing a broadened peak at $\delta 7.1$.

PROBLEM 13-1

Determine the number of different kinds of protons in each compound.

(a) 1-chloropropane **(b)** 2-chloropropane

(c) 2,2-dimethylbutane **(d)** 1-bromo-2-methylbenzene,



13-7 Areas of the Peaks

The area under a peak is proportional to the number of hydrogens contributing to that peak. For example, in the methyl *t*-butyl ether spectrum (Figure 13-11), the absorption of the *t*-butyl protons is larger and stronger than that of the methoxyl protons because there are three times as many *t*-butyl protons as methoxyl protons. We cannot simply compare peak heights, however; the *area* under the peak is proportional to the number of protons.

NMR spectrometers have **integrators** that compute the relative areas of peaks. The integrator draws a second trace (the integral trace) that rises when it goes over a peak. The amount the integral trace rises is proportional to the area of that peak. Newer digital instruments also print a number representing the area of each peak. These numbers correspond to the heights of the rises in an integral trace.

Neither an integral trace (shown in Figure 13-11) nor a digital integral can specifically indicate that methyl *t*-butyl ether has three methyl hydrogens and nine *t*-butyl hydrogens. Each simply shows that about three times as many hydrogens are represented by the peak at $\delta 1.2$ as are represented by the peak at $\delta 3.2$. We must interpret what the 3 : 1 ratio means in terms of the structure.

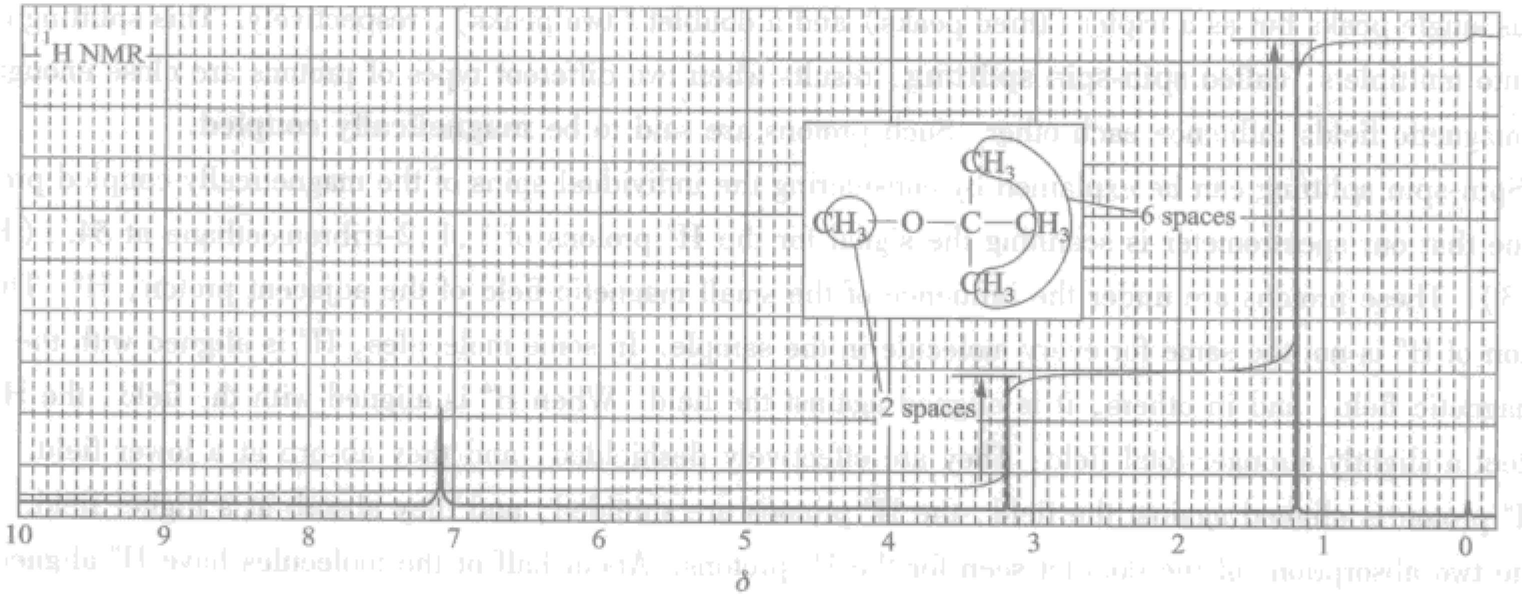


Figure 13-11 Integrated proton NMR spectrum of methyl *t*-butyl ether. In going over a peak, the integrator trace rises by an amount that is proportional to the area under the peak.

13-8 Spin-Spin Splitting

13-8A Theory of Spin-Spin Splitting

A proton in the NMR spectrometer is subjected to both the external magnetic field and the induced field of the shielding electrons. If there are other protons nearby, their small magnetic fields also affect the absorption frequencies of the protons we are observing. Consider the spectrum of 1,1,2-tribromoethane (Figure 13-12). As expected, there are two signals with areas in the ratio of 1 : 2. The smaller signal (H^a) appears at $\delta 5.7$, shifted

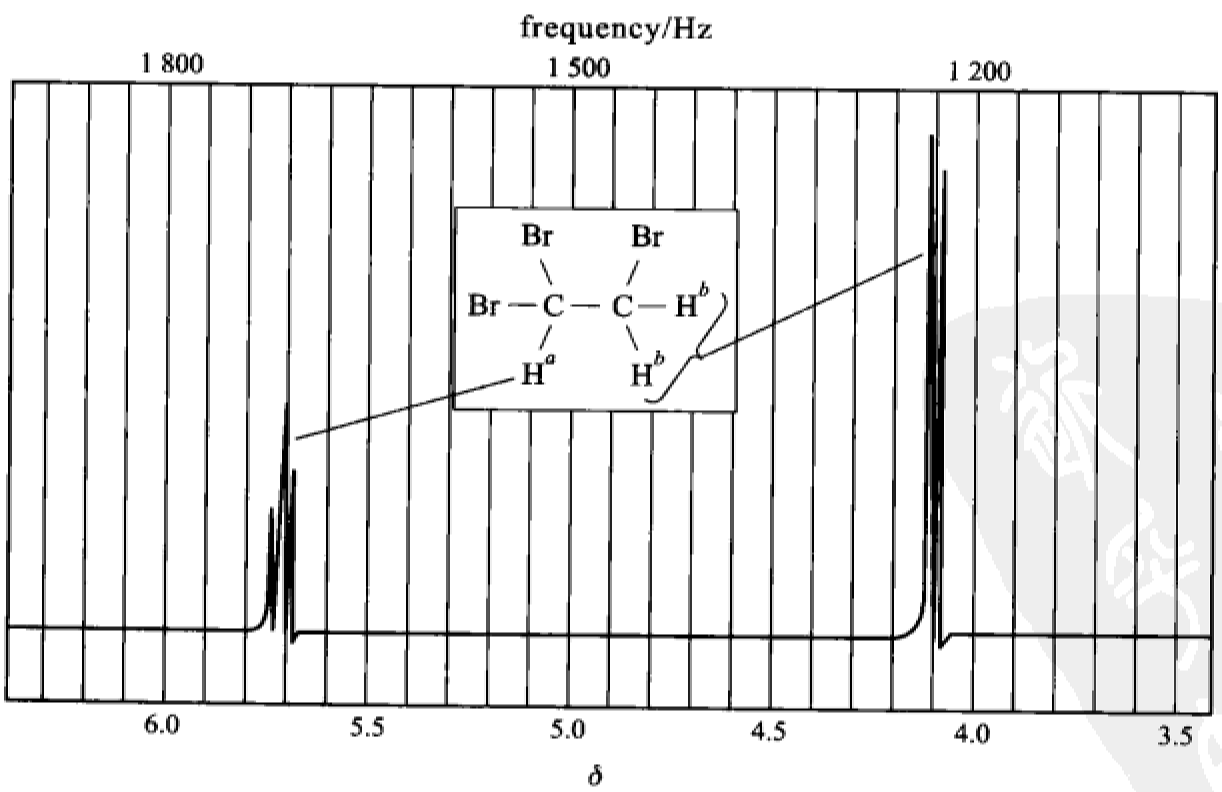


Figure 13-12 The proton NMR spectrum of 1,1,2-tribromoethane shows a triplet of area 1 at $\delta 5.7$ ($-CHBr_2$) and a doublet of area 2 at $\delta 4.1$ ($-CH_2Br$).

downfield by the two adjacent bromine atoms. The larger signal (H^b) appears at δ4.1. These signals do not appear as single peaks but as a triplet (three peaks) and a doublet (two peaks), respectively. This splitting of signals into multiplets, called **spin-spin splitting**, results when two different types of protons are close enough that their magnetic fields influence each other. Such protons are said to be **magnetically coupled.**

Spin-spin splitting can be explained by considering the individual spins of the magnetically coupled protons. Assume that our spectrometer is scanning the signal for the H^b protons of 1,1,2-tribromoethane at δ4.1 (Figure 13−13). These protons are under the influence of the small magnetic field of the adjacent proton, H^a. The orientation of H^a is not the same for every molecule in the sample. In some molecules, H^a is aligned with the external magnetic field, and in others, it is aligned against the field. When H^a is aligned with the field, the H^b protons feel a slightly stronger total field: They are effectively deshielded, and they absorb at a lower field. When the H^a proton is aligned against the field, the H^b protons are shielded, and they absorb at a higher field. These are the two absorptions of the doublet seen for the H^b protons. About half of the molecules have H^a aligned with the field and about half against the field, so the two absorptions of the doublet are nearly equal in area.

Spin-spin splitting is a reciprocal property. That is, if one proton splits another, the second proton must split the first.

Proton *a* in Figure 13−12 appears as a triplet (at δ5.7) because there are four permutations of the two H^b proton spins, with two of them giving the same magnetic field (Figure 13−14). When both H^b spins are aligned with the applied field, proton *a* is deshielded; when both H^b spins are aligned against the field, proton *a* is shielded; and when the two H^b spins are opposite each other (two possible permutations), they cancel each other

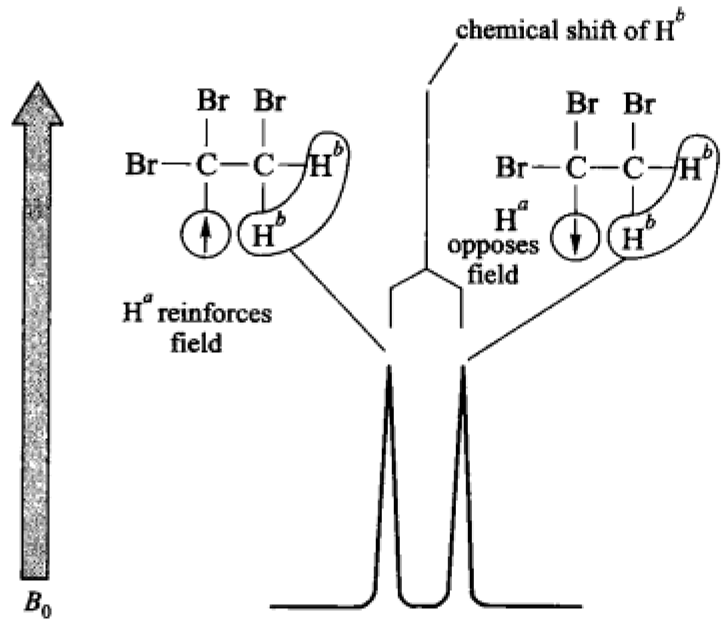


Figure 13−13 Splitting of the $-CH_2Br$ group in 1,1,2-tribromoethane. When the nearby H^a proton is aligned with the external magnetic field, it deshields H^b; when H^a is aligned against the field, it shields H^b.

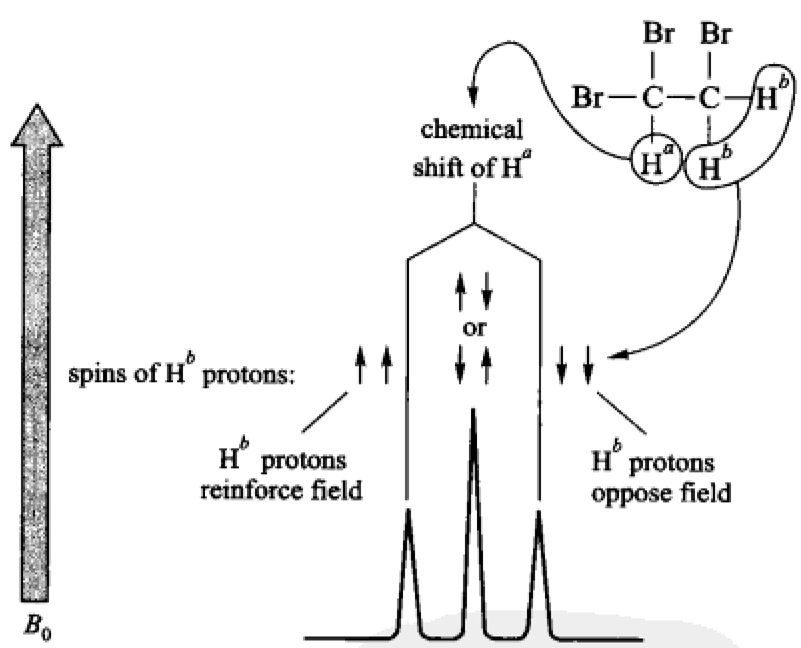


Figure 13−14 Splitting of the $-CHBr_2$ group in 1,1,2-tribromoethane. The H^a absorption is affected by the three combinations of H^b spins. When the H^b spins reinforce the external field, the H^a absorption occurs at a lower field. When the H^b spins oppose the external field, the H^a absorption occurs at a higher field. Two permutations, where the H^b proton spins cancel each other, allow H^a to absorb at its "normal" position. The peak area ratios are 1 : 2 : 1.

out. Three signals result, with the middle signal twice as large as the others because it corresponds to two possible spin permutations.

13−8B The *N*+1 Rule

The preceding analysis for the splitting of 1,1,2-tribromoethane can be extended to more complicated systems. In general, the multiplicity (number of peaks) of an NMR signal is given by the **$N+1$ rule**:

$N+1$ rule: If a signal is split by N equivalent protons, it is split into $N+1$ peaks.

The relative areas of the $N+1$ **multiplet** that results are approximately given by the appropriate line of *Pascal's triangle*:

Relative Peak Intensities of Symmetric Multiplets

Number of Equivalent Protons Causing Splitting	Number of Peaks (multiplicity)	Area Ratios (Pascal's triangle)
0	1(singlet, 单峰)	1
1	2(doublet, 双重峰)	1 1
2	3(triplet, 三重峰)	1 2 1
3	4(quartet, 四重峰)	1 3 3 1
4	5(quintet, 五重峰)	1 4 6 4 1
5	6(sextet, 六重峰)	1 5 10 10 5 1
6	7(septet, 七重峰)	1 6 15 20 15 6 1

Consider the splitting of the signals for the ethyl group in ethylbenzene (Figure 13−15). The methyl protons are split by two adjacent protons, and they appear upfield as a triplet of areas 1 : 2 : 1. The methylene (CH_2) protons are split by three protons, appearing farther downfield as a quartet of areas 1 : 3 : 3 : 1. This splitting pattern is typical for an ethyl group. Because ethyl groups are common, you should learn to recognize this familiar pattern. All five aromatic protons absorb close to 7.2 because the alkyl substituent has only a small effect on the chemical shifts of the aromatic protons. The aromatic protons split each other in a complicated manner.

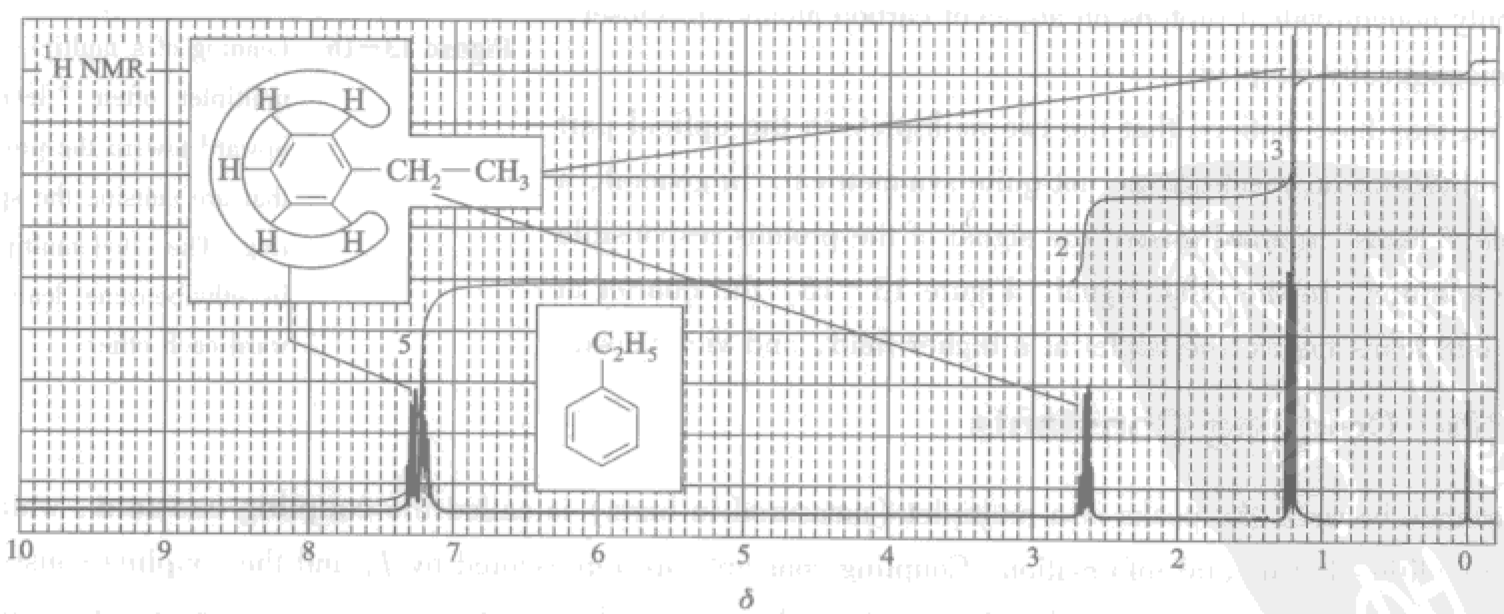


Figure 13−15 Proton NMR spectrum of ethylbenzene. The ethyl group appears as a triplet at δ1.2 (—CH_3) and a quartet at δ2.6 (—CH_2—). The aromatic protons appear as a multiplet near δ7.2.

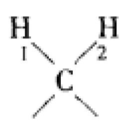
13-8C The Range of Magnetic Coupling

In ethylbenzene there is no spin-spin splitting between the aromatic protons and the protons of the ethyl group. These protons are not on adjacent carbon atoms, so they are too far away to be magnetically coupled. The magnetic coupling that causes spin-spin splitting takes place primarily through the bonds of the molecule. Most examples of spin-spin splitting involve coupling between protons that are separated by three bonds, so they are bonded to adjacent carbon atoms (vicinal protons).

Most spin-spin splitting is between protons on adjacent carbon atoms.

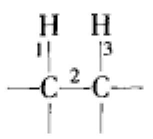
Protons bonded to the same carbon atom (geminal protons) can split each other *only if they are nonequivalent*. In most cases, protons on the same carbon atom are equivalent, and equivalent protons cannot split each other.

Bonded to the same carbon: two bonds between protons



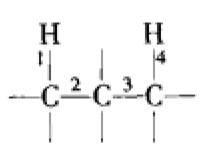
spin-spin splitting is normally observed (if nonequivalent)

Bonded to adjacent carbons: three bonds between protons



spin-spin splitting is normally observed (this is the most common case)

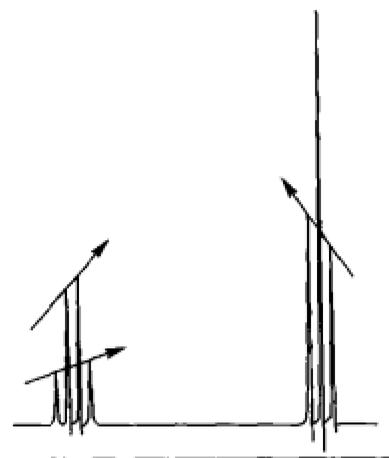
Bonded to nonadjacent carbons: four or more bonds between protons



spin-spin splitting is *not* normally observed

Protons separated by more than three bonds usually do not produce observable spin-spin splitting. Occasionally, such "long-range coupling" does occur, but these cases are unusual. For now, we consider only nonequivalent protons on adjacent carbon atoms (or closer) to be magnetically coupled.

You may have noticed that the two multiplets in the upfield part of the ethylbenzene spectrum are not quite symmetrical. In general, a multiplet "leans" upward toward the signal of the protons responsible for the splitting. In the ethyl signal (Figure 13-16) the quartet at lower field leans toward the triplet at a higher field, and vice versa.



characteristic ethyl group

Figure 13-16 Leaning of a multiplet. A multiplet often "leans" upward toward the protons that are causing the splitting. The ethyl multiplets in ethylbenzene lean toward each other.

13-8D Coupling Constants

The distance between the peaks of a multiplet (measured in hertz) is called the **coupling constant**, which can provide additional structural information. Coupling constants are represented by J, and the coupling constant between H^a and H^b is represented by J_{ab}. In complicated spectra with many types of protons, groups of neighboring protons can sometimes be identified by measuring their coupling constants. Multiplets that have the same coupling constant may arise from adjacent groups of protons that split each other, because any two magnetically coupled protons must have equal effects on each other.

The magnetic effect that one proton has on another depends on the bonds connecting the protons, but it does not depend on the strength of the external magnetic field. For this reason, the coupling constant (measured in hertz) does not vary with the field strength of the spectrometer. Figure 13-17 shows typical values of coupling constants.

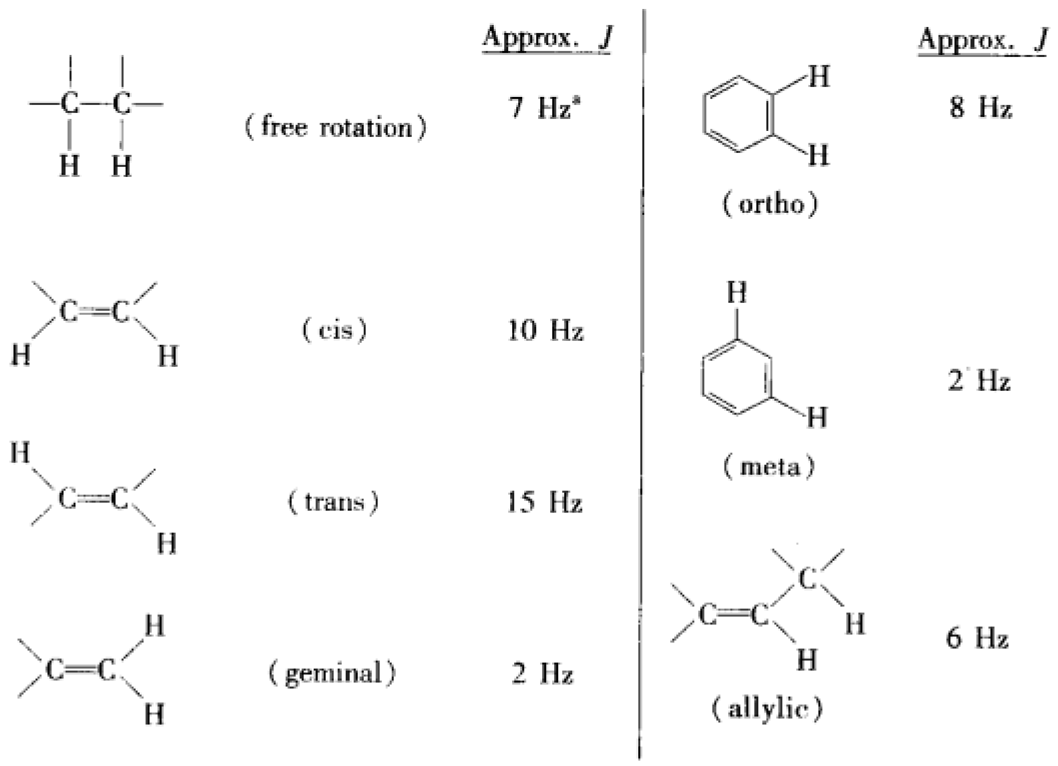


Figure 13-17 Typical values of proton coupling constants.

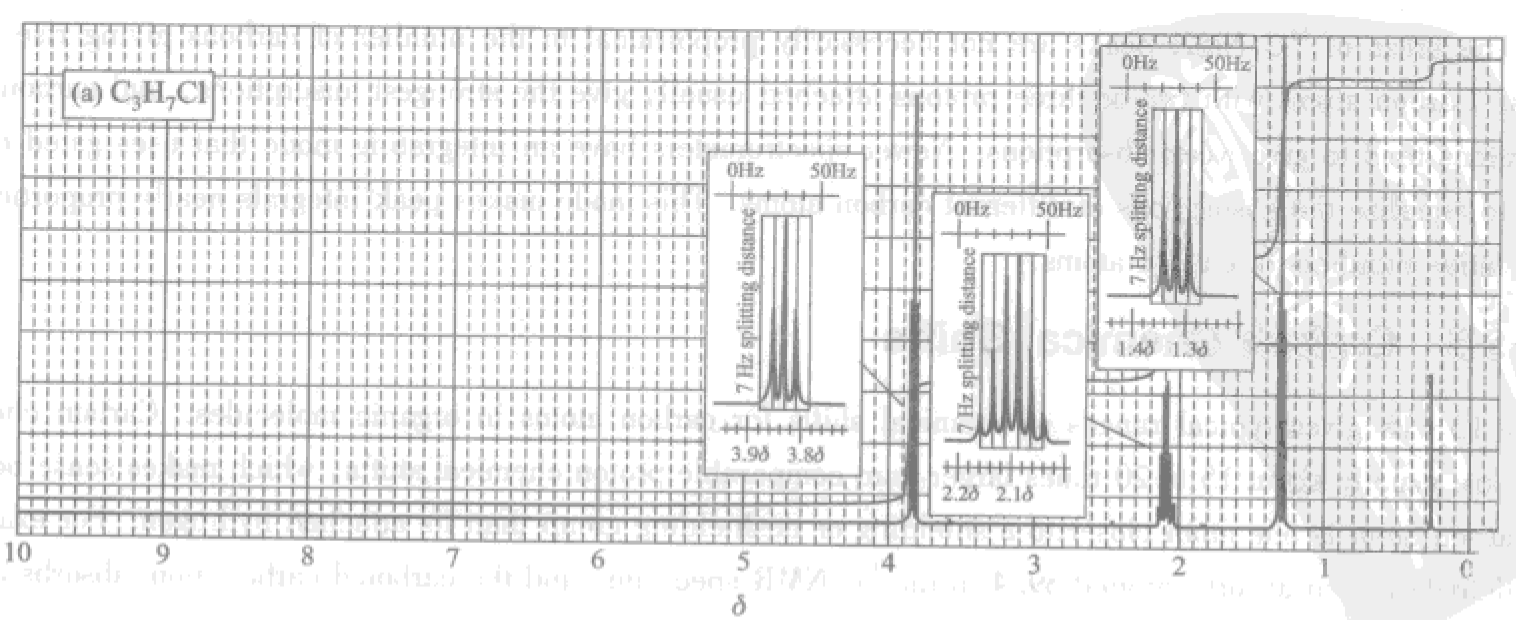
[a]The value of 7 Hz in an alkyl group is averaged for rapid rotation about the carbon-carbon bond. If rotation is hindered by a ring or bulky groups, other splitting constants may be observed.

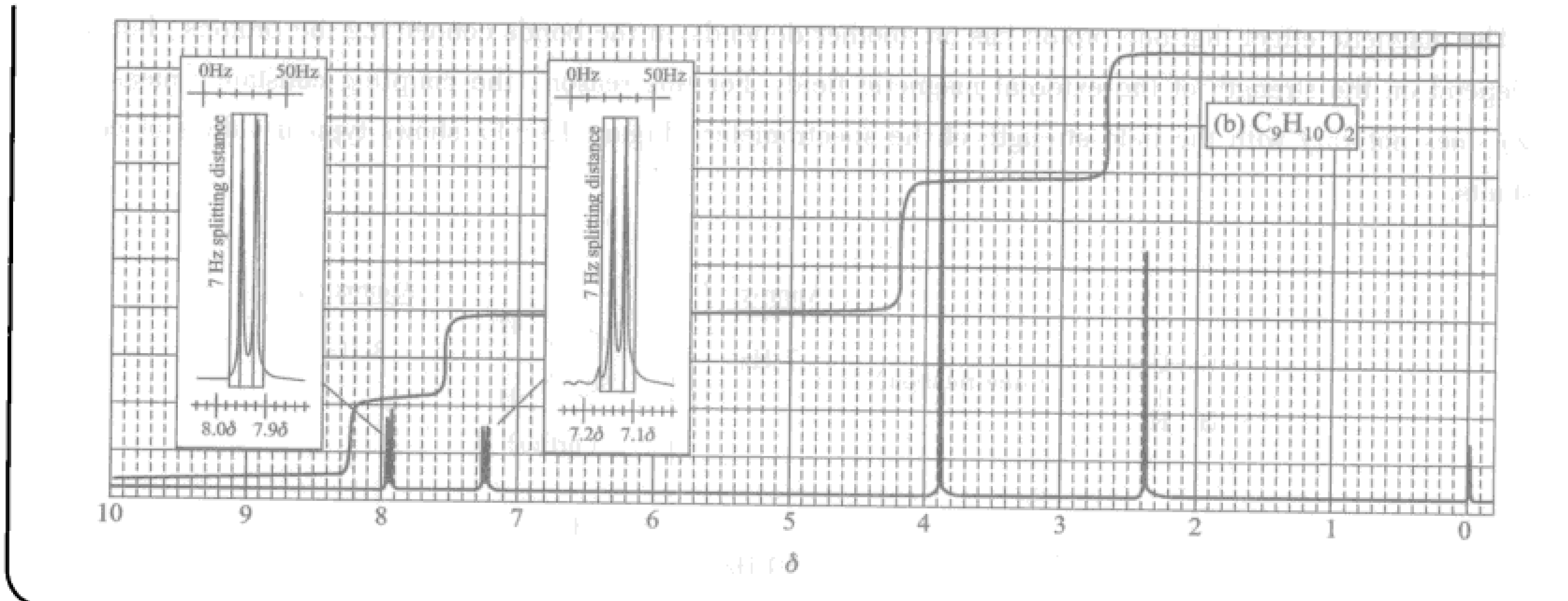
PROBLEM 13-2

An unknown compound (C_3H_2NCl) shows moderately strong IR absorptions around 1650 cm^{-1} and 2200 cm^{-1}. Its NMR spectrum consists of two doublets ($J = 14$ Hz) at δ5.9 and δ7.1. Propose a structure consistent with these data.

PROBLEM 13-3

Two spectra are shown. Propose a structure that corresponds to each spectrum.





13-9 Carbon-13 NMR Spectroscopy

The development of Fourier transform NMR spectroscopy made carbon NMR (^{13}C NMR or CMR) possible, and high-field superconducting spectrometers allowed it to become nearly as convenient as proton NMR (^{1}H NMR). Carbon NMR determines the magnetic environments of the carbon atoms themselves. Carbonyl carbon atoms, alkyne carbon atoms, and aromatic carbon atoms all have characteristic chemical shifts in the ^{13}C NMR spectrum.

13-9A Sensitivity of Carbon NMR

Carbon NMR took longer than proton NMR to become a routine technique because carbon NMR signals are much weaker than proton signals. About 99% of the carbon atoms in a natural sample are the isotope ^{12}C. This isotope has an even number of protons and an even number of neutrons, so it has no magnetic spin and cannot give rise to NMR signals. The less abundant isotope ^{13}C has an odd number of neutrons, giving it a magnetic spin of $\frac{1}{2}$, just like a proton. Because only 1% of the carbon atoms in a sample are the magnetic ^{13}C isotope, the sensitivity of ^{13}C NMR is decreased by a factor of 100. In addition, the gyromagnetic ratio of ^{13}C is only one-fourth that of the proton, so the ^{13}C resonance frequency (at a given magnetic field) is only one-fourth of that for ^{1}H NMR. The smaller gyromagnetic ratio leads to a further decrease in sensitivity.

The areas of ^{13}C NMR peaks are not necessarily proportional to the number of carbons giving rise to the peaks. Carbon atoms with two or three protons attached usually give the strongest absorptions, and carbons with no protons tend to give weak absorptions. Newer spectrometers have an integrating mode that uses gated decoupling to equalize the absorptions of different carbon atoms. This mode makes peak integrals nearly proportional to the relative numbers of carbon atoms.

13-9B Carbon Chemical Shifts

Figure 13-18 gives typical ranges of chemical shifts for carbon atoms in organic molecules. Carbon chemical shifts are usually about 15 to 20 times larger than comparable proton chemical shifts, which makes sense because the carbon atom is one atom closer to a shielding or deshielding group than its attached hydrogen. For example, an aldehyde proton absorbs around δ9.4 in the ^{1}H NMR spectrum, and the carbonyl carbon atom absorbs around 180 downfield from TMS in the ^{13}C spectrum.

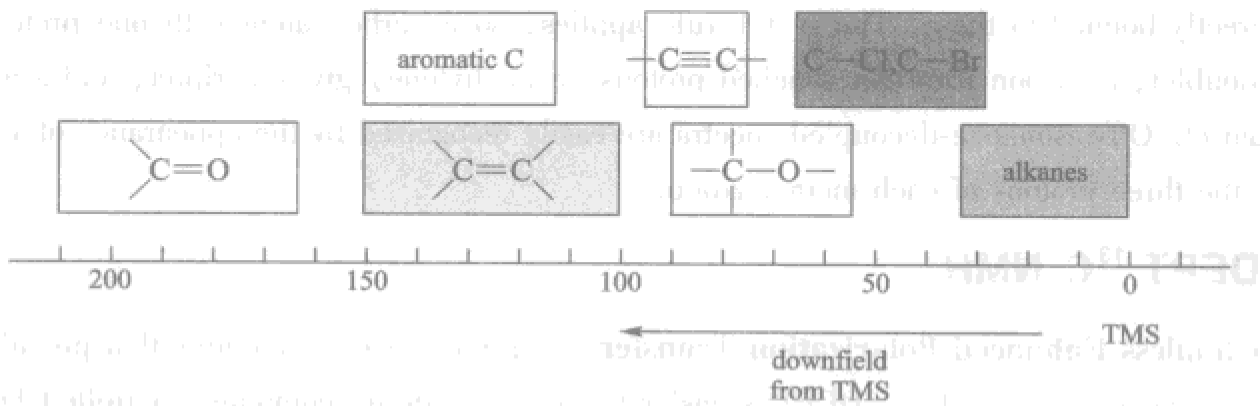


Figure 13-18 Table of approximate chemical shift values for ^{13}C NMR. Most of these values for a carbon atom are about 15 to 20 times the chemical shift of a proton if it were bonded to the carbon atom.

13-9C Spin-Spin Splitting

^{13}C NMR splitting patterns are quite different from those observed in ^{1}H NMR. Only 1% of the carbon atoms in the ^{13}C NMR sample are magnetic, so there is only a small probability that an observed ^{13}C nucleus is adjacent to another ^{13}C nucleus. Therefore, carbon-carbon splitting can be ignored. Carbon-hydrogen coupling is common, however. Most carbon atoms are bonded directly to hydrogen atoms or are sufficiently close to hydrogen atoms for carbon-hydrogen spin-spin coupling to be observed. Extensive carbon-hydrogen coupling produces splitting patterns that can be complicated and difficult to interpret.

Proton Spin Decoupling To simplify ^{13}C NMR spectra, they are commonly recorded using **proton spin decoupling**, where the protons are continuously irradiated with a broadband ("noise") proton transmitter. As a result, all the protons are continuously in resonance, and they rapidly flip their spins. The carbon nuclei see an *average* of the possible combinations of proton spin states. Each carbon signal appears as a single, unsplit peak because any carbon-hydrogen splitting has been eliminated.

Off-Resonance Decoupling Proton spin decoupling produces spectra that are very simple, but some valuable information is lost in the process. **Off-resonance decoupling** simplifies the spectrum but allows some of the splitting information to be retained (Figure 13-19). With off-resonance decoupling, the ^{13}C nuclei are split only by

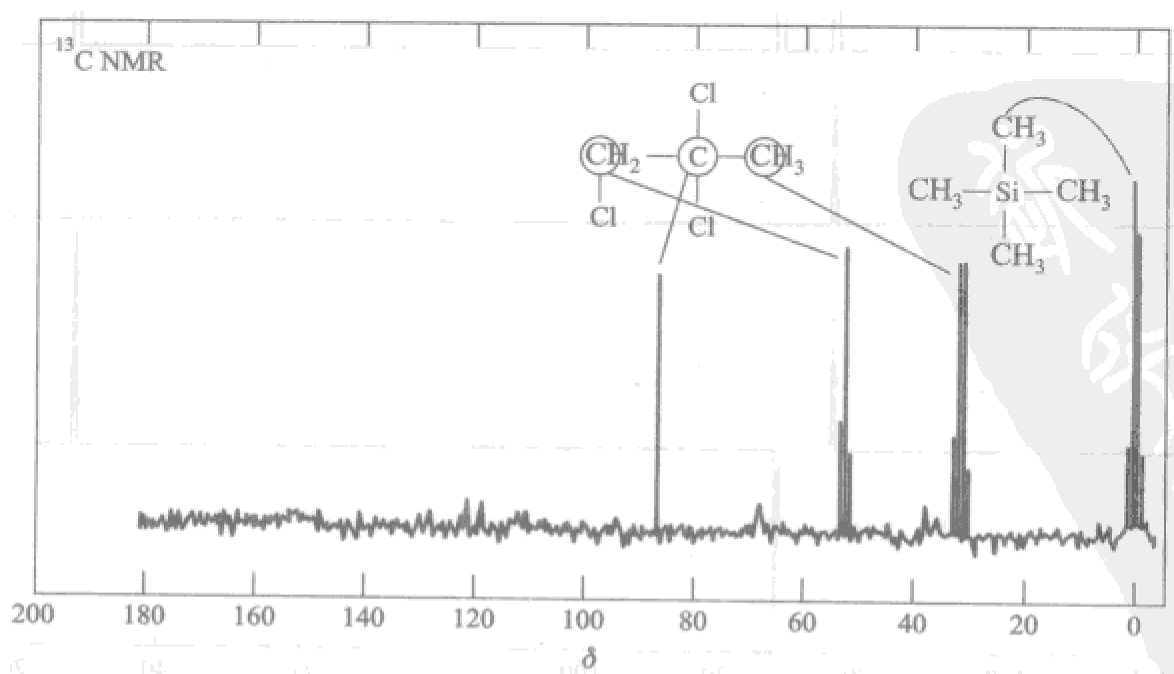


Figure 13-19 Off-resonance-decoupled ^{13}C NMR spectrum of 1,2,2-trichloropropane. The CCl_2 group appears as a singlet, the CH_2Cl group as a triplet, and the CH_3 group as a quartet.

.ne protons directly bonded to them. The $N+1$ rule applies, so a carbon atom with one proton (a methine) appears as a doublet, a carbon with two attached protons (a methylene) gives a triplet, and a methyl carbon is split into a quartet. Off-resonance-decoupled spectra are easily recognized by the appearance of TMS as a quartet at 0, split by the three protons of each methyl group.

13-9D DEPT ^{13}C NMR

DEPT (Distortionless Enhanced Polarization Transfer) is a more recent technique that provides the same information as off-resonance decoupling. DEPT is easier to run on modern, computer-controlled Fourier-transform spectrometers. DEPT gives better sensitivity, and it avoids overlapping multiplets because all the peaks remain decoupled singlets.

Each ^{13}C nucleus is magnetically coupled to the protons bonded to it. Under the right circumstances, this magnetic coupling allows the transfer of polarization from the protons to the carbon nucleus. The number of protons bonded to the ^{13}C nucleus determines how this polarization transfer occurs. A DEPT experiment usually includes three spectral scans:

1. The normal decoupled scan, in which each type of ^{13}C nucleus appears as a singlet.

2. The DEPT-90 scan, in which *only* the CH (methine) carbons bonded to exactly one proton appear.

3. The DEPT-135 scan, in which the CH_3 (methyl) groups and CH (methine) groups appear normally, and the CH_2 groups give negative peaks. Carbons that are bonded to no protons do not appear.

This information allows us to distinguish among carbons bonded to 0, 1, 2, or 3 hydrogen atoms:

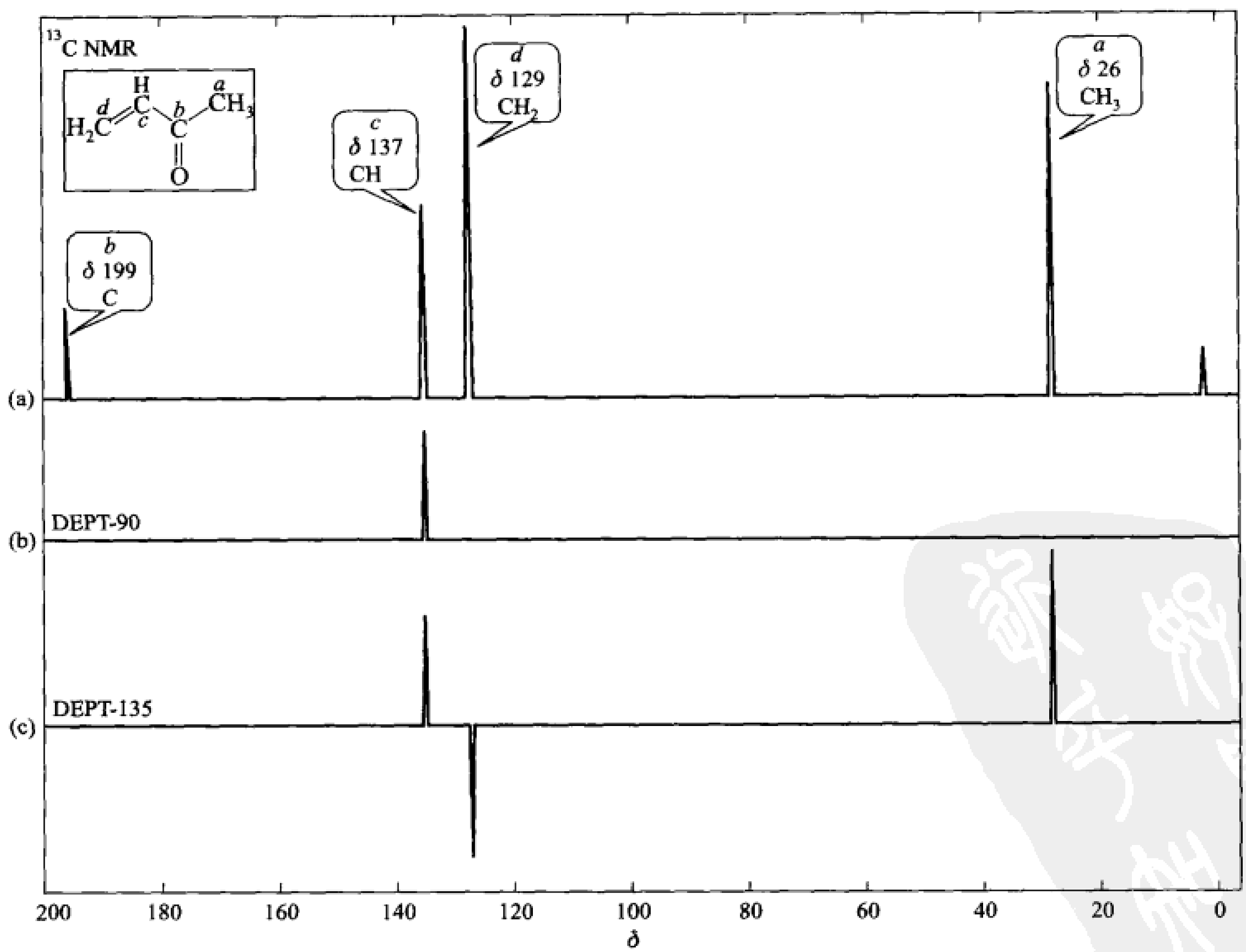


Figure 13-20 ^{13}C NMR spectrum and DEPT spectra of but-3-en-2-one.

- Carbons with no H's appear only in the normal spectrum, but not in either DEPT spectrum.
- Methine carbons (CH) give normal positive peaks in all three spectra.
- Methylene (CH_2) carbons give normal peaks in the normal spectrum, no peaks in the DEPT-90 spectrum, and negative peaks in the DEPT-135 spectrum.
- Methyl (CH_3) carbons give normal peaks in the normal spectrum, no peaks in the DEPT-90 spectrum, and normal peaks in the DEPT-135 spectrum.

Figure 13−20 shows the normal decoupled ^{13}C NMR spectrum of but-3-en-2-one (a), plus the DEPT-90 spectrum (b), and the DEPT-135 spectrum (c). Note that the carbonyl carbon (C_b, no protons) appears only in the regular spectrum. C_c, with 1 proton, appears normally in all the spectra. C_d, with two protons, appears as a negative peak in the DEPT-135 spectrum. C_a the methyl carbon with three protons, vanishes in the DEPT-90 spectrum but appears as a normal peak in the DEPT-135 spectrum.

13−10 Interpreting Carbon NMR Spectra

Interpreting ^{13}C NMR spectra uses the same principles as interpreting ^1H NMR spectra. In fact, carbon spectra are often easier to interpret. The ^{13}C NMR spectrum provides the following information:

1. The *number of different signals* implies how many different types of carbons are present.
2. The *chemical shifts* of those signals suggest what types of functional groups contain those carbon atoms.
3. The *peak areas* (in the integrating mode) imply how many carbons of each type are present.
4. The *splitting of signals* in the off-resonance-decoupled spectrum or the DEPT-90 and DEPT-135 spectra indicate how many protons are bonded to each carbon atom.

In the following example (Figure 13−21), only the broadband-decoupled spectrum is provided. The off-resonance multiplicity of each peak is indicated: (s) = singlet, (d) = doublet, (t) = triplet, and (q) = quartet.

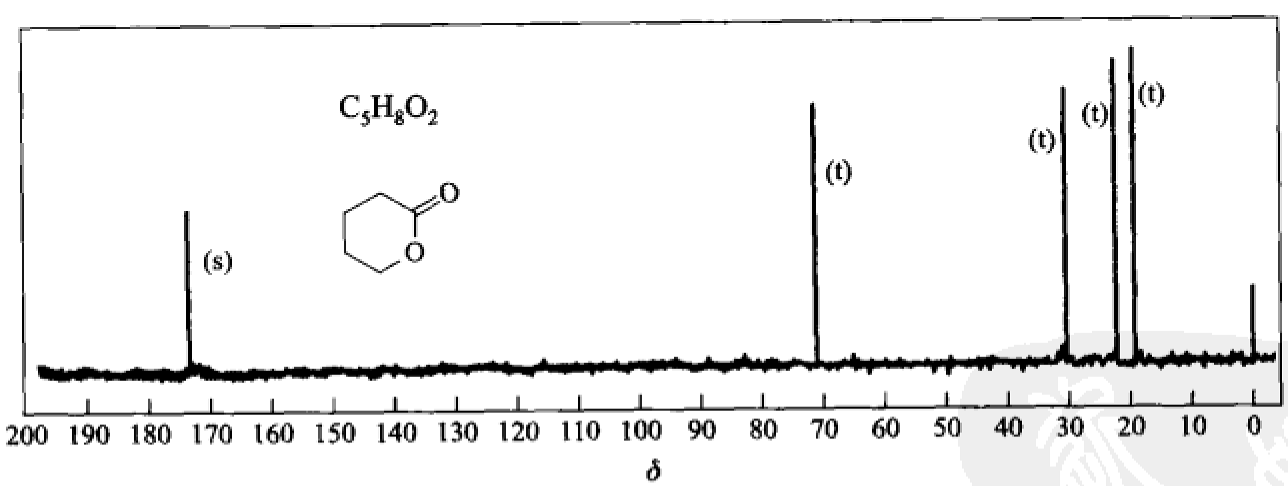
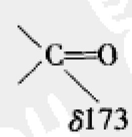
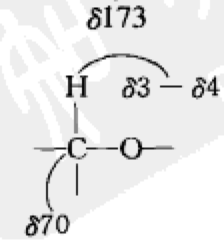


Figure 13−21 Off-resonance-decoupled and broadband-decoupled spectra of δ-valerolactone, molecular formula $C_5H_8O_2$.



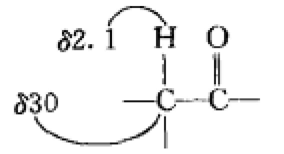


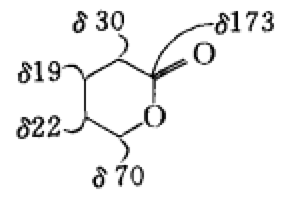
Let's consider how we might solve this structure, given only the ^{13}C NMR spectrum and the molecular formula. The signal at 173 is appropriate for a carbonyl carbon. The off-resonance-decoupled spectrum shows a singlet at 173, implying that no hydrogens are bonded to the carbonyl carbon.

The chemical shift of the next absorption is about 70. This is about 20 times the chemical shift of a proton on a carbon bonded to an electronegative element. The molecular formula

implies that the electronegative element must be oxygen. Since the signal at 70 is a triplet in the off-resonance-decoupled spectrum, this carbon must be a methylene (—CH_2—) group.

The signal at 30 corresponds to a carbon atom bonded to a carbonyl group. Remember that a proton on a carbon adjacent to a carbonyl group absorbs around 2.1, and we expect the carbon to have a chemical shift about 15 to 20 times as large. This carbon atom is a methylene group, as shown by the triplet in the off-resonance-decoupled spectrum.



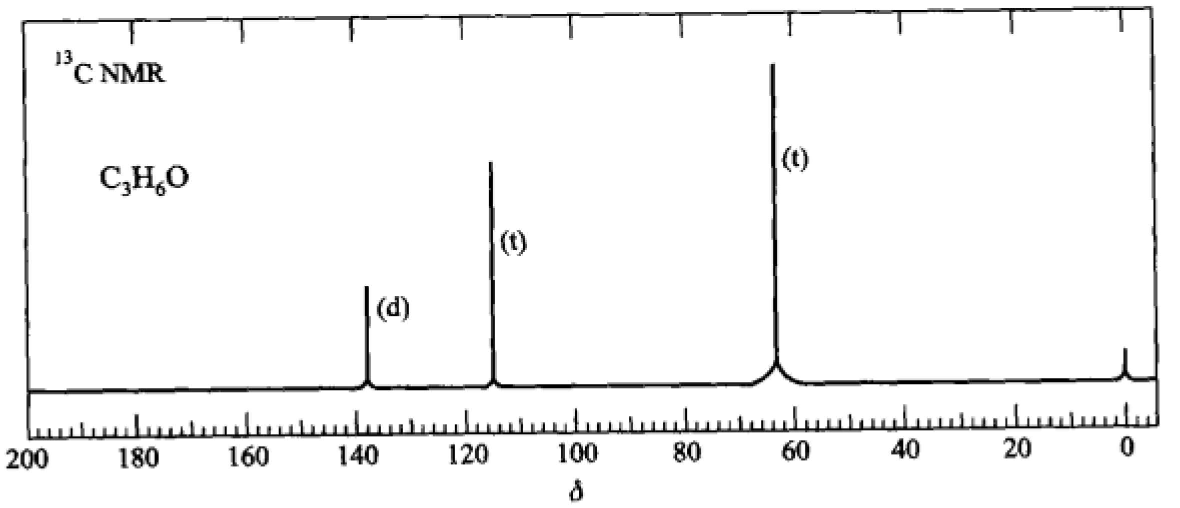


The two signals at 19 and 22 are from carbon atoms that are not directly bonded to any deshielding group, although the carbon at 22 is probably closer to one of the oxygen atoms. These are also triplets in the off-resonance-decoupled spectrum and they correspond to methylene groups.

The molecular formula $C_5H_8O_2$ implies the presence of two elements of unsaturation. The carbonyl (C=O) group accounts for one, but there are no more carbonyl groups and no double-bonded alkene carbon atoms. The other element of unsaturation must be a ring. Combining the partial structures into a ring gives the complete structure.

PROBLEM 13-4

A bottle of allyl bromide was found to contain a large amount of an impurity. A careful distillation separated the impurity, which has the molecular formula C_3H_6O. The following ^{13}C NMR spectrum of the impurity was obtained:



(a) Propose a structure for this impurity.
(b) Assign the peaks in the ^{13}C NMR spectrum to the carbon atoms in the structure.
(c) Suggest how this impurity arose in the allyl bromide sample.

13-11 Introduction to Mass Spectrometry

Mass spectrometry (MS) provides the molecular weight and valuable information about the molecular formula, using a very small sample. High-resolution mass spectrometry (HRMS) can provide an accurate molecular formula. The mass spectrum also provides structural information that can confirm a structure derived from NMR and IR spectroscopy.

Mass *spectrometry* is fundamentally different from *spectroscopy*. Spectroscopy involves the absorption (or emission) of light over a range of wavelengths. Mass spectrometry does not use light at all. In the mass spectrometer, a sample is struck by high-energy electrons, breaking the molecules apart. The masses of the fragments are measured, and this information is used to reconstruct the molecule. The process is similar to analyzing a vase by shooting it with a rifle, then weighing all the pieces.

13-11A The Mass Spectrometer

A **mass spectrometer** ionizes molecules in a high vacuum, sorts the ions according to their masses, and records the abundance of ions of each mass. A **mass spectrum** is the graph plotted by the mass spectrometer, with the masses plotted as the x axis and the relative number of ions of each mass on the y axis. Several methods are used to ionize samples and then to separate ions according to their masses. We will discuss only the most common techniques, *electron impact ionization* for forming the ions, and *magnetic deflection* for separating the ions.

Electron Impact Ionization In the **ion source**, the sample is bombarded by a beam of electrons. When an electron strikes a neutral molecule, it may ionize that molecule by knocking out an additional electron.

$$e^- + M \longrightarrow [M]^{+\cdot} + 2e^-$$

When a molecule loses one electron, it then has a positive charge and one unpaired electron. The ion is therefore a **radical cation**, which has seven electrons around it. This unusual cation is represented by $[\mathbf{M}]^{+}\cdot$, with the + indicating the positive charge and the · indicating the unpaired electron.

In addition to ionizing a molecule, the impact of an energetic electron may break it apart. This **fragmentation** process gives a characteristic mixture of ions. The radical cation corresponding to the mass of the original molecule is called the **molecular ion**, abbreviated $\mathbf{M}^+$. The ions of smaller molecular weights are called *fragments*.

Separation of Ions of Different Masses Once ionization and fragmentation have formed a mixture of ions, these ions are separated and detected. The most common type of mass spectrometer, shown in Figure 13-22, separates ions by *magnetic deflection*.

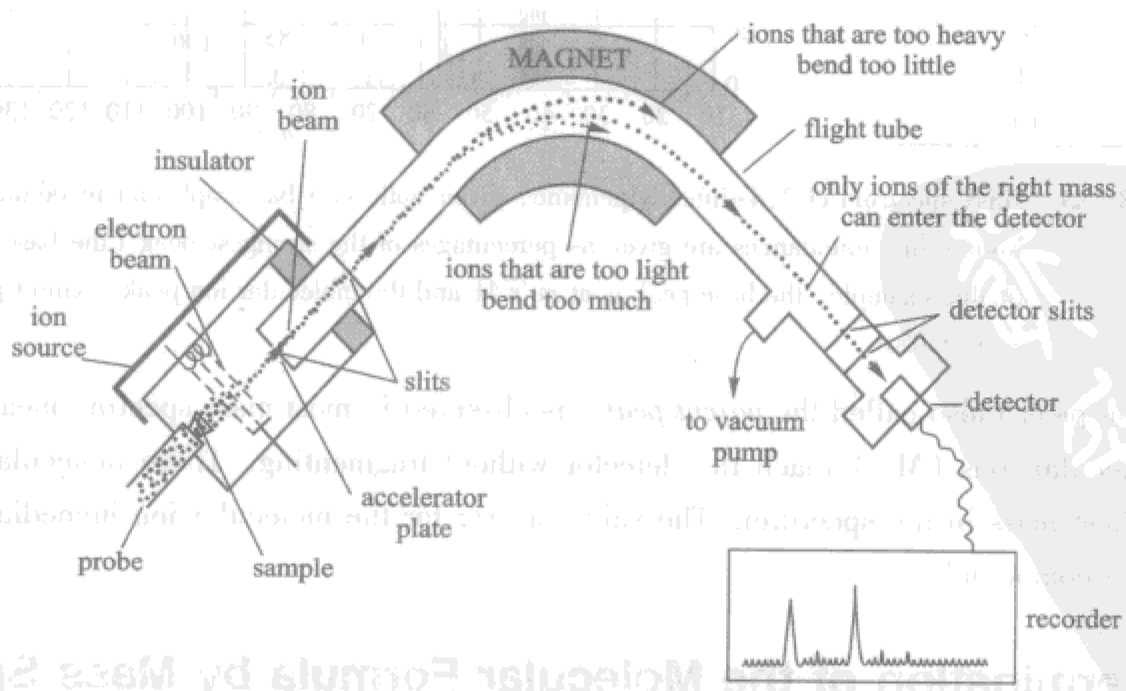


Figure 13-22 Diagram of a mass spectrometer. A beam of electrons causes molecules to ionize and fragment. The mixture of ions is accelerated and passes through a magnetic field, where the paths of lighter ions are bent more than those of heavier ions. By varying the magnetic field, the spectrometer plots the abundance of ions of each mass.

After ionization, the positively charged ions are attracted to a negatively charged accelerator plate, which has a narrow slit to allow some of the ions to pass through. The ion beam enters an evacuated flight tube, with a curved portion positioned between the poles of a large magnet. When a charged particle passes through a magnetic field, a transverse force bends its path. The path of a heavier ion bends less than the path of a lighter ion.

The exact radius of curvature of an ion's path depends on its mass-to-charge ratio, symbolized by $\boldsymbol{m/z}$. In this expression, m is the mass of the ion (in amu) and z is its charge in units of the electronic charge. The vast majority of ions have a charge of $+1$, so we consider their path to be curved by an amount that depends only on their mass.

At the end of the flight tube is another slit, followed by an ion detector connected to an amplifier. At any given magnetic field, only ions of one particular mass are bent exactly the right amount to pass through the slit and enter the detector. The detector signal is proportional to the number of ions striking it. By varying the magnetic field, the spectrometer scans all the possible ion masses and produces a graph of the number of ions of each mass.

13−11B The Mass Spectrum

The mass spectrometer usually plots the spectrum as a graph on a computer screen. This information is tabulated, and the spectrum is printed as a bar graph or as a table of relative abundances (Figure 13−23). In the printed mass spectrum, all the masses are rounded to the nearest whole-number mass unit. The peaks are assigned abundances as percentages of the strongest peak, called the **base peak**. Notice that *the base peak does not necessarily correspond to the mass of the molecular ion.* It is simply the strongest peak, making it easy for other peaks to be expressed as percentages.

m/z	Abundance (% of base peak)
39	62
41	100 (base peak)
42	24
43	90
56	23
57	50
85	11
100 (M^+)	10

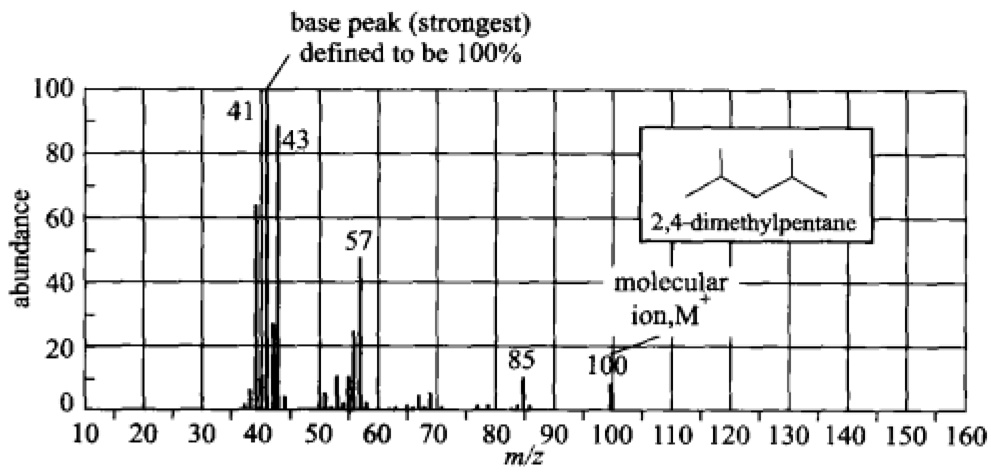


Figure 13−23 Mass spectrum of 2,4-dimethylpentane, given both as a bar graph and in tabular form. Notice that abundances are given as percentages of the strongest peak (the base peak). In this example, the base peak is at m/z 41 and the molecular ion peak (parent peak) is at m/z 100.

A molecular ion peak (also called the *parent peak*) is observed in most mass spectra, meaning that a detectable number of molecular ions (M^+) reach the detector without fragmenting. These molecular ions are usually the particles of highest mass in the spectrum. The value of m/z for the molecular ion immediately gives the molecular weight of the compound.

13−12 Determination of the Molecular Formula by Mass Spectrometry

13−12A High-Resolution Mass Spectrometry

Although mass spectra usually show the particle masses rounded to the nearest whole number, the masses are not

really integral. The ^{12}C nucleus is *defined* to have a mass of exactly 12 atomic mass units (u), and all other nuclei have masses based on this standard. For example, a proton has a mass of about 1, but not exactly: Its mass is 1.007 825 u. Table 13-3 shows the atomic masses for the most common isotopes found in organic compounds.

TABLE 13-3 "Exact" Masses of Common Isotopes

Isotope	Atomic Mass u
^{12}C	12.000000
^{1}H	1.007825
^{16}O	15.994914
^{14}N	14.003050

Determination of a molecular formula is possible using a **high-resolution mass spectrometer** (HRMS), one that uses extra stages of electrostatic or magnetic focusing to form a very precise beam and to detect particle masses to an accuracy of about 1 part in 20000. A mass determined to several significant figures using an HRMS is called an *exact mass*. Although it is not really exact, it is much more accurate than the usual integral mass numbers. Comparing the exact mass with masses calculated by molecular formula makes it possible to identify the correct formula.

Consider a molecular ion with a mass of 44. This approximate molecular weight might correspond to C_3H_8 (propane), C_2H_4O (acetaldehyde), CO_2, or CN_2H_4. Each of these molecular formulas corresponds to a different exact mass:

C_3H_8	C_2H_4O	CO_2	CN_2H_4
3C 36.00000	2C 24.00000	1C 12.00000	1C 12.00000
8H 8.06260	4H 4.03130		4H 4.03130
	1O 15.99490	2O 31.98983	2N 28.00610
44.06260	44.02620	43.98983	44.03740

If the HRMS measured the exact mass of this ion as 44.029 mass units, we would conclude that the compound has a molecular formula of C_2H_4O, because the mass corresponding to this formula is closest to the observed value. Published tables of exact masses are available for comparison with values obtained from the HRMS. Depending on the completeness of the tables, they may include sulfur, halogens or other elements.

13-12B Use of Heavier Isotope Peaks

Whether or not a high-resolution mass spectrometer is available, molecular ion peaks often provide information about the molecular formula. Most elements do not consist of a single isotope, but contain heavier isotopes in varying amounts. These heavier isotopes give rise to small peaks at higher mass numbers than the major M^+ molecular ion peak. A peak that is one mass unit heavier than the M^+ peak is called the **M + 1 peak**; two units heavier, the **M + 2 peak**; and so on. Table 13-4 gives the isotopic composition of some common elements, showing how they contribute to M + 1 and M + 2 peaks.

TABLE 13-4 Isotopic Composition of Some Common Elements

Element	M^+		M+1		M+2	
hydrogen	^{1}H	100.0%				
carbon	^{12}C	98.9%	^{13}C	1.1%		
nitrogen	^{14}N	99.6%	^{15}N	0.4%		
oxygen	^{16}O	99.8%			^{18}O	0.2%
sulfur	^{32}S	95.0%	^{33}S	0.8%	^{34}S	4.2%
chlorine	^{35}Cl	75.5%			^{37}Cl	24.5%
bromine	^{79}Br	50.5%			^{81}Br	49.5%
iodine	^{127}I	100.0%				

Ideally, we could use the isotopic compositions in Table13-4 to determine the entire molecular formula of a compound, by carefully measuring the abundances of the M^+, M + 1, and M + 2 peaks. In practice, however,

there are background peaks at every mass number. These background peaks are often similar in intensity to the M + 1 peak, preventing an accurate measurement of the M + 1 peak. High-resolution mass spectrometry is much more reliable.

Some elements (particularly S, Cl, Br, I, and N) are recognizable from molecular ion peaks, however, as the spectra shown next illustrate. A typical compound with no sulfur, chlorine, or bromine has a small M + 1 peak and an even smaller M + 2 peak. If a compound contains sulfur, the M + 2 peak is larger than the M + 1 peak: about 4% of the M^+ peak. If chlorine is present, the M + 2 peak is about a third as large as the M^+ peak. If bromine is present, the M^+ and M + 2 ions have about equal abundances; the molecular ion appears as a doublet separated by two mass units, with one mass corresponding to ^{79}Br and one to ^{81}Br.

Iodine is recognized by the presence of the iodonium ion, I^+, at *m/z* 127. This clue is combined with a characteristic 127-unit gap in the spectrum corresponding to loss of the iodine radical. Nitrogen (or an odd number of nitrogen atoms) is suggested by an odd molecular weight. Stable compounds containing only carbon, hydrogen, and oxygen have even molecular weights.

Recognizable elements in the mass spectrum

Br	M + 2 as large as M^+
Cl	M + 2 a third as large as M^+
I	I^+ at 127; large gap
N	odd M^+
S	M + 2 larger than usual (4% of M^+)

13-13 Fragmentation Patterns in Mass Spectrometry

In addition to the molecular formula, the mass spectrum provides structural information. An electron with a typical energy of 6 740 kJ/mol has far more energy than needed to ionize a molecule. The impact forms the radical cation, and it often breaks a bond to give a cation and a radical. The resulting cation is observed by the mass spectrometer, but the uncharged radical is not accelerated or detected. We can infer the mass of the uncharged radical from the amount of mass lost from the molecular ion to give the observed cation fragment.

Ionization

$$\mathrm{R:R'} + e^- \longrightarrow [\mathrm{R\cdot R'}]^{+\cdot} + 2e^-$$

radical cation (自由基正离子)
(molecular ion)

Fragmentation

$$[\mathrm{R \frown R'}]^{+\cdot} \longrightarrow \mathrm{R}^+ + \cdot\mathrm{R'}$$

cation fragment (observed) — radical fragment (not observed)

This bond breaking does not occur randomly; it tends to form the most stable fragments. By knowing what stable fragments result from different kinds of compounds, we can recognize structural features and use the mass spectrum to confirm a proposed structure.

13-13A Mass Spectra of Alkanes

The mass spectrum of *n*-hexane (Figure 13-24) shows several characteristics typical of straight-chain alkanes.

The base peak (m/z 57) corresponds to loss of an ethyl group, giving an ethyl radical and a butyl cation. The neutral ethyl radical is not detected, because it is not charged and is not accelerated or deflected.

m/z of the charged fragment on this side of the broken bond → 57

$$[CH_3CH_2CH_2CH_2{-}|{-}CH_2CH_3]^{+\cdot} \longrightarrow CH_3CH_2CH_2CH_2^+ + \cdot CH_2CH_3$$

hexane radical cation, M^+ 86 → 1-butyl cation, detected at m/z 57 + ethyl radical (29), not detected

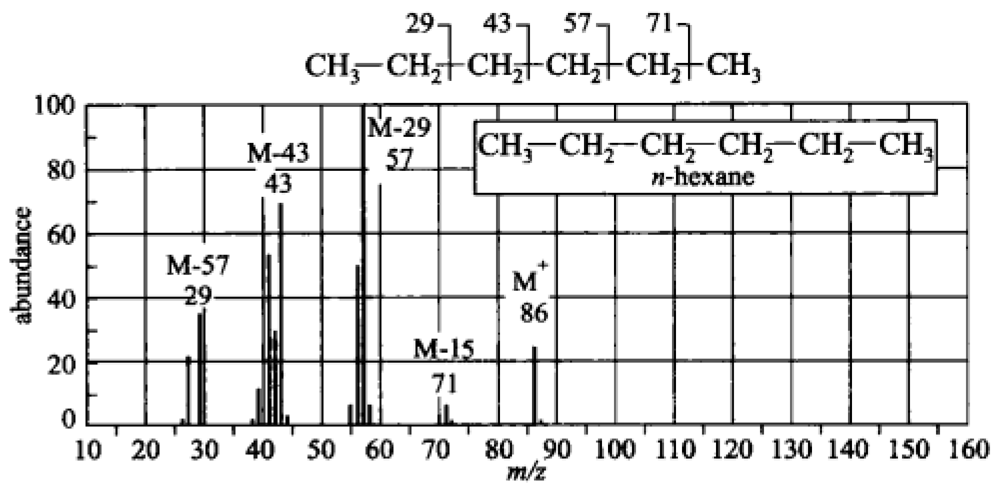


Figure 13-24 Mass spectrum of *n*-hexane. Groups of ions correspond to loss of one-, two-, three-, and four-carbon fragments.

A similar fragmentation gives an ethyl cation and a butyl radical. In this case, the ethyl fragment (m/z 29) is detected.

$$[CH_3CH_2CH_2CH_2{-}\overset{29}{|}{-}CH_2CH_3]^{+\cdot} \longrightarrow CH_3CH_2CH_2CH_2\cdot + {}^+CH_2CH_3$$

hexane radical cation, M^+ 86 → 1-butyl radical (57), not detected + ethyl cation, detected at m/z 29

Symmetric cleavage of hexane gives a propyl cation and a propyl radical.

$$[CH_3CH_2CH_2{-}\overset{43}{|}{-}CH_2CH_2CH_3]^{+\cdot} \longrightarrow CH_3CH_2CH_2^+ + \cdot CH_2CH_2CH_3$$

hexane radical cation, M^+ 86 → propyl cation, detected at m/z 43 + propyl radical (43), not detected

Cleavage to give a pentyl cation (m/z 71) and a methyl radical is weak because the methyl radical is less stable than a substituted radical. Cleavage to give a methyl cation (m/z 15) and a pentyl radical is not visible because the methyl cation is less stable than a substituted cation. The stability of the cation is apparently more important than the stability of the radical, since a weak peak appears corresponding to loss of a methyl radical, but we see no cleavage to give a methyl cation.

$$[CH_3CH_2CH_2CH_2CH_2{-}\overset{71}{|}{-}CH_3]^{+\cdot} \longrightarrow CH_3CH_2CH_2CH_2CH_2^+ + \cdot CH_3$$

hexane radical cation, M^+ 86 → pentyl cation, weak at m/z 71 + methyl radical (15), not detected

$$[CH_3CH_2CH_2CH_2CH_2 \text{—|—} CH_3]^{+\cdot} \xrightarrow{-15 \text{ (not formed)}} \!\!\!\!\!\!\!\!\not\;\;\; CH_3CH_2CH_2CH_2CH_2\cdot \; + \; {}^+CH_3$$

hexane radical cation M^+ 86 — pentyl radical (71) not detected — methyl cation (too unstable)

Cation and radical stabilities help to explain the mass spectra of branched alkanes as well. Fragmentation of a branched alkane commonly occurs at a branch carbon atom to give the most highly substituted cation and radical.

PROBLEM 13-5

Show the fragmentation that accounts for the cation at m/z 57 in the mass spectrum of 2-methylpentane.

PROBLEM 13-6

Show the fragmentations that give rise to the peaks at m/z 43, 57, and 85 in the mass spectrum of 2,4-dimethylpentane (Figure 13-23).

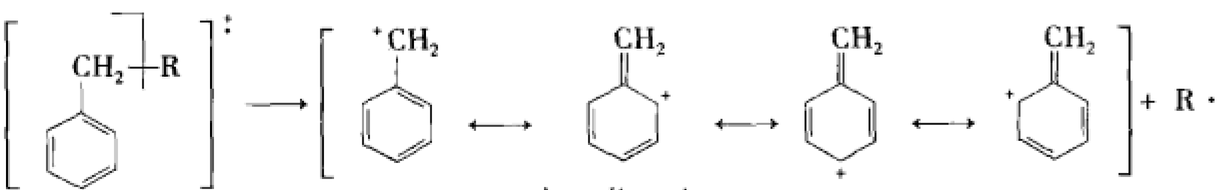
13-13B Fragmentation Giving Resonance-Stabilized Cations

Fragmentation in the mass spectrometer gives resonance-stabilized cations whenever possible. The most common fragmentation of alkenes is cleavage of an allylic bond to give a resonance-stabilized allylic cation.

$$[R\text{—}CH\text{=}CH\text{—}CH_2 \text{—|—} R']^{+\cdot} \longrightarrow [R\text{—}CH\text{=}CH\text{—}\overset{+}{C}H_2 \longleftrightarrow R\text{—}\overset{+}{C}H\text{—}CH\text{=}CH_2] + \cdot R'$$

allylic cation

Compounds containing aromatic rings tend to fragment at the carbon (called a *benzylic* carbon) next to the aromatic ring. Such a cleavage forms a resonance-stabilized benzylic cation.



benzylic cation

Ethers, amines, and carbonyl compounds can also fragment to give resonance-stabilized cations. The oxygen and nitrogen atoms in these compounds have nonbonding electrons that can stabilize the positive charge of a cation through resonance forms with octets on all the atoms. We will see examples of these favorable fragmentations in later chapters covering the chemistry of these functional groups.

Ketones and aldehydes: loss of alkyl groups to give acylium ions

$$\left[R\text{—}\overset{\overset{\Large O}{\|}}{C} \text{—|—} R'\right]^{+\cdot} \longrightarrow R\text{—}C\equiv O^+ \; + \cdot R'$$

even — acylium ion (odd)

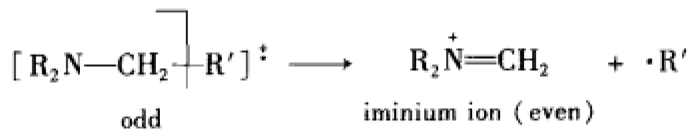
Ethers: loss of an alkyl group

$$[R\text{—}CH_2\text{—}O \text{—|—} R']^{+\cdot} \longrightarrow R\text{—}CH\text{=}\overset{+}{O}H \; + \cdot R'$$

even — stabilized cation (odd)

or: α cleavage

Amines: α cleavage to give stabilized cations



PROBLEM 13−7

Ethers are not easily differentiated by their infrared spectra, but they tend to form predictable fragments in the mass spectrum. The following compounds give similar but distinctive mass spectra.

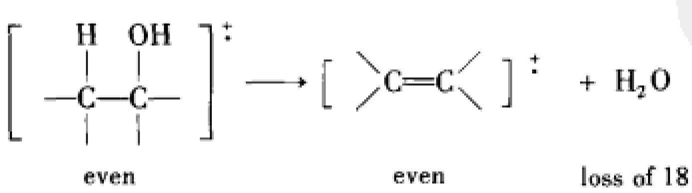
butyl propyl ether　　　butyl isopropyl ether

Both compounds give prominent peaks at m/z 116, 73, 57, and 43. But one compound gives a distinctive strong peak at 87, and the other compound gives a strong peak at 101. Determine which compound gives the peak at 87 and which one gives the peak at 101. Propose fragmentations to account for the ions at m/z 116, 101, 87, and 73.

13−13C Fragmentation Splitting Out a Small Molecule; Mass Spectra of Alcohols

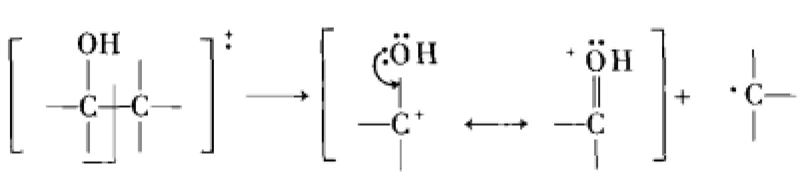
Mass spectral peaks are often seen corresponding to loss of small, stable molecules. Loss of a small molecule is usually indicated by a peak with an even mass number, corresponding to loss of an even mass number. A radical cation may lose water (18), CO (28), CO_2 (44), and even ethene (28) or other alkenes. The most common example is the loss of water from alcohols, which occurs so readily that the molecular ion is often weak or absent. The peak corresponding to loss of water (the M-18 peak) is usually strong, however.

Alcohols often lose water.



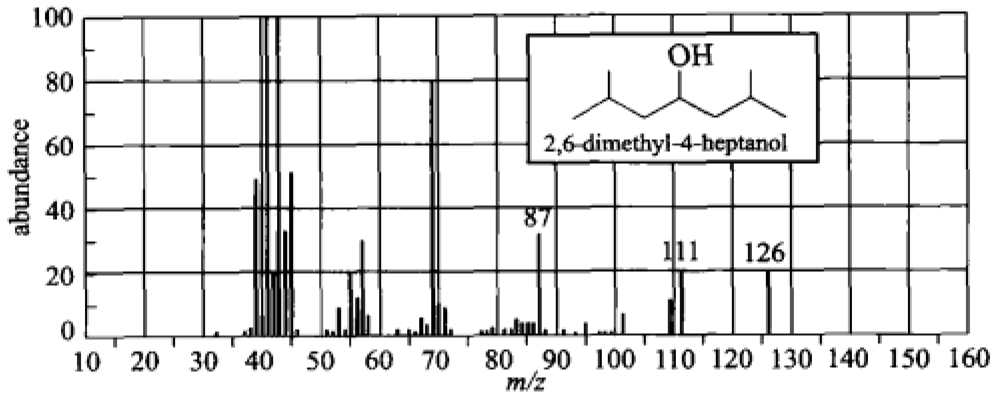
In addition to losing water, alcohols commonly fragment next to the carbinol carbon atom to give a resonance-stabilized carbocation. This fragmentation is called an *alpha cleavage* because it breaks the bond next to the carbon bearing the hydroxyl group.

α cleavage of an alcohol



PROBLEM 13-8

Account for the peaks at m/z 87, 111, and 126 in the mass spectrum of 2,6-dimethyl-4-heptanol.



Summary in Chinese

本章概要

一、核磁共振谱(nuclear magnetic resonance spectroscopy)

1. 核磁共振基本原理：具有奇数原子序数或奇数相对原子质量的原子核，如^{1}H、^{13}C、^{15}N、^{19}F、^{29}Si、^{31}P等，都具有球形电荷分布，都是自旋的，由此产生一个沿着原子核自旋轴的微小磁场，称之为磁矩(magnetic moment)。在外磁场作用下，原子核处于两种自旋态，一种是原子核自旋磁场与外磁场同向平衡，称为α-自旋态，能量较低；另一种是自旋磁场与外磁场反向平衡，称为β-自旋态，能量较高。两种自旋态的能量差(ΔE)很小，只要吸收长波低能量的无线电波范围内的辐射光，原子核就可从低能量的α-自旋态跃迁到高能量的β-自旋态，称为核磁共振。因此，核磁共振谱本质上也是一种吸收光谱。原子核跃迁所需要的辐射光的频率(ν)与外磁场磁感应强度(B_0)成正比，当满足下列关系式时，辐射光的能量才能被吸收，产生核磁共振。

$$\Delta E = h\nu = \gamma \frac{h}{2\pi}B_0 \qquad \nu = \frac{1}{2\pi}\gamma B_0$$

式中：h 为普朗克常数；γ 为磁旋比；因原子核不同而异。

目前实验室中使用的核磁共振仪一般是固定电磁波辐射频率，改变外磁场感应强度即扫场方式，来获得核磁共振谱。

2. 屏蔽效应(shielded)与化学位移(chemical shift)：在外磁场作用下，原子核周围的电子在垂直于磁场的平面做圆周运动，产生感应磁场，当其方向与外磁场方向相反，可使原子核实际受到的磁场小于外磁场，这种作用称为电子对核的屏蔽效应。当辐射频率恒定时，只有增加外磁场强度，补偿了被屏蔽掉的磁场(σB_0，σ 为屏蔽常数)，被屏蔽的原子核才可能发生核磁共振吸收。原子核周围电子密度越大，屏蔽效应越大，发生共振吸收所需要的外磁场强度越大。分子中处于不同化学环境的原子核受到的屏蔽作用大小不同，产生共振吸收的外磁场强度不同，在谱图中给出不同的信号位置，称为化学位移(一般以 δ 表示)。通常^{1}H NMR 谱的化学位移以四甲基硅(TMS)为参照物，将其化学位移定为零，其他质子的化学位移可由下式得出：

$$\delta = \frac{\nu_{TMS} - \nu_s}{\nu_0} \times 10^6$$

式中：ν_s 为样品信号频率；ν_{TMS} 为四甲基硅的信号频率；ν_0 为仪器电磁波辐射频率，频率单位 Hz。

3. 影响质子化学位移的主要结构因素：其他原子或基团的诱导效应和 π 电子环流是影响质子化学位移的主要结构因素。质子直接与电负性大的原子成键，或者与质子相连的碳原子上有电负性大的原子时，可使质子周围电子密度减小，产生去屏蔽作用，共振吸收向低场移动。质子与电负性基团相隔的键越多，化学位移值越小。由于 π 电子循环流动所产生的诱导磁场对于与双键和苯环直接相连的质子具有去屏蔽作用，使与 sp^2 杂化碳原子相连的质子的化学位移向低场移动。π 电子环流和羰基吸电子诱导效应两种去屏蔽作用使与羰基相连的质子的化学位移明显向低场移动。形成氢键可使质子去屏蔽，化学位移向低场移动。总之，质子的化学位移反映了氢的化学环境，由此可推测分子结构。不同质子的化学位移见 Table 13－2。

4. 磁等性质子与磁不等性质子：分子中化学环境完全相同的质子称为磁等性质子，其化学位移相同，在 ^{1}H NMR 谱中只给出一个峰；化学环境不同的质子称为磁不等性质子，其化学位移不同。因此，^{1}H NMR 谱图中出峰的组数反映了分子中化学环境不同的质子数目。

5. 积分曲线与质子数目：每一组峰的积分曲线高度与引起该峰的磁等性质子的数目成比例，各组峰的积分曲线高度比代表了各种类型的质子数目之比。

6. 自旋裂分与偶合常数：质子除受周围电子云的作用之外，还受到分子中相邻的磁不等性质子两种自旋态的小磁场的作用，这种原子核间的相互作用称为自旋偶合，由自旋偶合产生的信号裂分称为自旋裂分。两种磁不等性质子相隔少于或等于三个共价单键时，质子间的自旋偶合作用强，能够观察到信号裂分；大于三个共价单键时，自旋偶合作用很弱，一般观察不到自旋裂分。磁等性质子间不发生自旋偶合。吸收峰裂分的间距称为偶合常数（J，单位 Hz）。偶合常数大小与偶合质子间的键数、相互取向及官能团的类型有关。相互自旋偶合的质子所引起的两组峰的偶合常数相等。分子中某个质子与 N 个磁等性质子自旋偶合，该质子核磁共振信号裂分为 $N+1$ 重峰，称为 $N+1$ 规律。裂分后各峰的相对强度之比等于二项式 $(a+b)^n$ 展开式各项系数之比。由峰的裂分数目可知相邻氢的数目，而由峰裂分的形状和偶合常数可判断相邻氢的类型。

7. ^{13}C NMR 谱基本概念：^{13}C 核的自然丰度为 1.08%，旋磁比 γ 仅为 ^{1}H 核的 1/4，^{13}C 谱的灵敏度约等于 ^{1}H 核的 1/5 700。因此，必须通过信号多次累加，提高信噪比，才能观察到 ^{13}C NMR 谱。以四甲基硅的碳的化学位移（δ_C）为零，大多数有机化合物的 ^{13}C 化学位移在 $0 \sim 250 \times 10^{-6}$ 范围内。碳的化学位移大约是与其相连的氢的化学位移的 15～20 倍。常见有机化合物的 ^{13}C 化学位移范围见 Figure 13－18。由碳的化学位移可知其化学环境，从而推测其在碳链中的位置。目前实验室中使用的核磁共振仪所测得的 ^{13}C NMR谱中，峰的面积与碳的种类有关，而与引起该峰的碳的数目不成比例关系。

8. ^{13}C NMR 实验技术：质子自旋去偶（proton spin decoupling），又称质子噪声去偶或宽带去偶，所有磁不等性碳核都以单峰出现在 ^{13}C NMR 谱中，由出峰数目可知分子中不同类型碳原子数目；偏共振去偶（off-resonance decoupling）技术去掉了 ^{13}C—^{1}H 二键以上的偶合，但保留了一键偶合产生的裂分，如碳原子与 N 个氢原子直接相连，则该碳原子的峰的裂分数为（$N+1$），由此可推断碳原子上连接氢的数目；DEPT 技术（distortionless enhanced polarization transfer），称为无畸变极化转移增强技术。利用此技术可得到两种谱图，在 DEPT 90°谱图中，只有 CH 出正峰，而在 DEPT 135°谱图中，CH 和 CH_3 出正峰，CH_2 出倒峰，季碳原子在 DEPT 谱中不出峰，CH、CH_2、CH_3 在 DEPT 谱中都是单峰。

二、质谱（mass spectrometry）

1. 质谱的基本原理：样品分子在高真空下，经高能电子束轰击时，分子失去一个外层电子而变成分子离子（M^+），分子离子可在键合较弱处断裂成不同碎片，有些碎片带有正电荷。分子离子和带电荷的碎片在电场、磁场作用下，按其质量与所带电荷之比（m/z）的大小分离得到质谱。

2. 质谱的应用：质谱中分子离子（M^+）的质量数代表了化合物的相对分子质量，高分辨质谱（high-resolution mass spectrum）能够给出化合物的精确相对分子质量；用 M+2 同位素峰判断分子中是否存在 Br（M+2 峰与 M^+ 峰等高）、Cl（M+2 峰为 M^+ 峰的 1/3）和 S（M+2 峰约为 M^+ 峰的 4%）。如 M^+ 为奇数

表明分子中含奇数个氮原子。分子中含 I 时出现 $m/z=127$ 特征峰,并且出现 m/z 相差 127 的峰。分析质谱中不同 m/z 的碎片质量和强度,结合化学键断裂规律,可推断化合物的分子结构。

Essential Problem-Solving Skills in Chapter 13

1. Given a structure, determine which protons are equivalent and which are nonequivalent; predict the number of signals and their approximate chemical shifts.
2. Given the chemical shifts of absorptions, suggest likely types of protons.
3. Use the integral trace to determine the relative numbers of different types of protons.
4. Predict which protons in a structure will be magnetically coupled, and predict the number of peaks and approximate coupling constants of their multiplets.
5. Use proton spin-spin splitting patterns to determine the structure of alkyl and other groups.
6. Draw the general features of the NMR spectrum of a given compound.
7. Predict the approximate chemical shifts of carbon atoms in a given compound. Given the chemical shifts of ^{13}C absorptions, suggest likely types of carbons.
8. Use the off-resonance decoupled or DEPT ^{13}C spectrum to determine the number of hydrogens bonded to a given carbon.
9. Combine the chemical shifts, integrals, and spin-spin splitting patterns in the NMR spectrum with information from infrared and mass spectra to determine the structures of organic compounds.
10. Determine molecular weights from mass spectra.
11. When possible, use mass spectra to recognize the presence of Br, Cl, I, N, and S atoms.
12. Predict the major ions from fragmentation of alkanes, alkenes, and alcohols.

Study Problems

13-9 A graduate student was following a procedure to make 3-propylcyclohexa-1,4-diene. During the workup procedure, his research adviser called him into her office. By the time the student returned to his bench, the product had warmed to a higher temperature than recommended. He isolated the product, which gave the appropriate =C—H stretch in the IR, but the C=C stretch appeared around 1 630 cm^{-1} as opposed to the literature value of 1 650 cm^{-1} for the desired product. The mass spectrum showed the correct molecular weight, but the base peak was at M-29 rather than at M-43 as expected.

(a) Should he have his IR recalibrated or should he repeat the experiment, watching the temperature more carefully? What does the 1 630 cm^{-1} absorption suggest?

(b) Draw the structure of the desired product, and propose a structure for the actual product.

(c) Show why he expected the MS base peak to be at M-43, and show how your proposed structure would give an intense peak at M-29.

13-10 An unknown compound has the molecular formula $C_9H_{11}Br$. Its proton NMR spectrum shows the following absorptions:

singlet, δ7.1, integral 4.4 cm

singlet, δ2.3, integral 13.0 cm

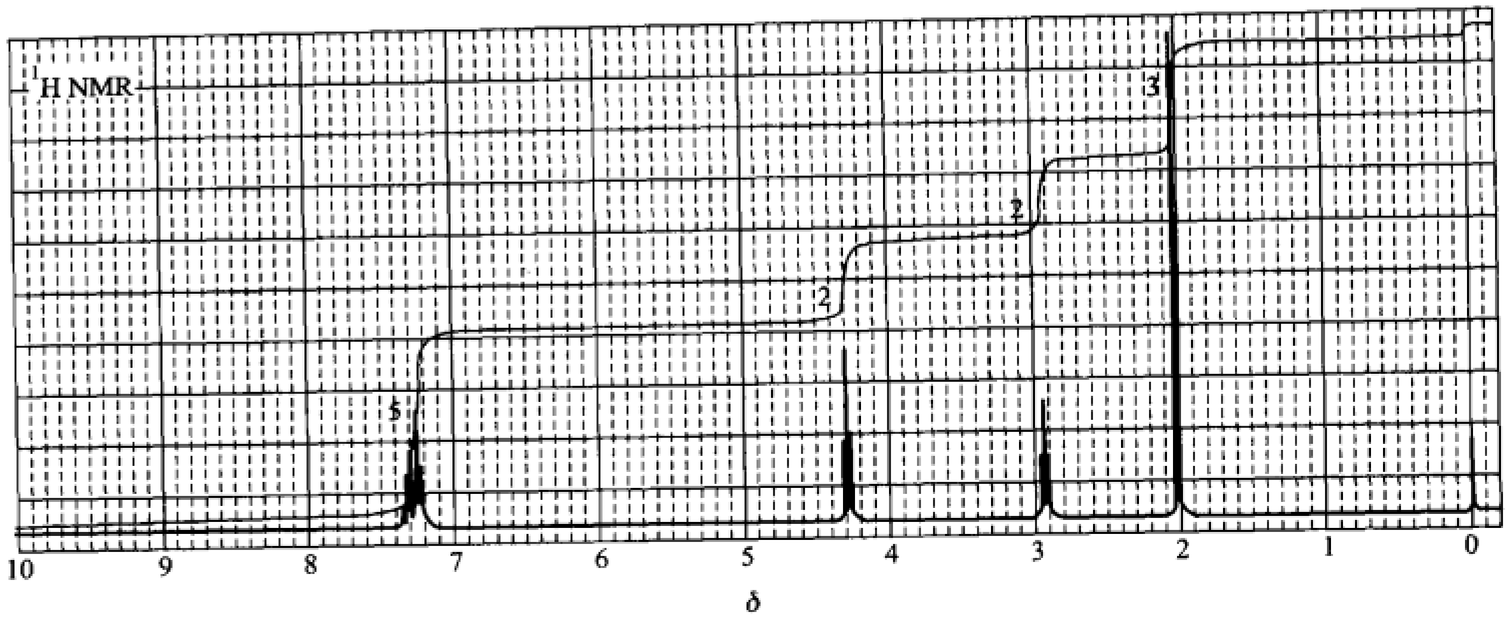
singlet, δ2.2, integral 6.7 cm

Propose a structure for this compound.

13-11 A compound ($C_{10}H_{12}O_2$) whose spectrum is shown here was isolated from a reaction mixture containing 2-phenylethanol and acetic acid.

(a) Propose a structure for this compound.

(b) Assign peaks to show which protons give rise to which signals in the spectrum.

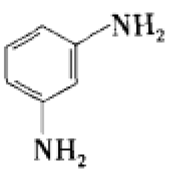


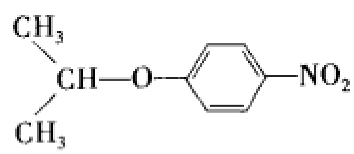
13−12 Sketch your predictions of the proton NMR spectra of the following compounds.

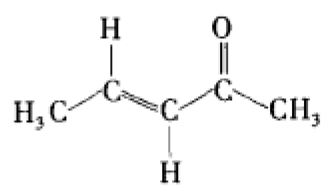
(a) $CH_3—O—CH_2CH_3$

(b) $(CH_3)_2CH—C(=O)—CH_3$

(c) $Cl—CH_2—CH_2—CH_2—Cl$

(d) 

(e) 

(f) 

13−13 Tell precisely how you would use the proton NMR spectra to distinguish between the following pairs of compounds.

(a) 1-bromopropane and 2-bromopropane

(b) $CH_3—CH_2—C(=O)—CH_3$ and $(CH_3)_2CH—C(=O)—CH_3$

(c) $CH_3—CH_2—O—C(=O)—CH_3$ and $CH_3—CH_2—C(=O)—O—CH_3$

(d) $CH_3—CH_2—C≡C—CH_3$ and $CH_3—CH_2—C(=O)—CH_3$

13−14 For each compound shown below,

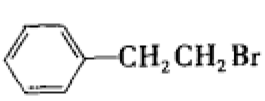
(1) Sketch the ^{13}C NMR spectrum (totally decoupled, with a singlet for each type of carbon), showing approximate chemical shifts.

(2) Show the multiplicity expected for each signal in the off-resonance-decoupled spectrum.

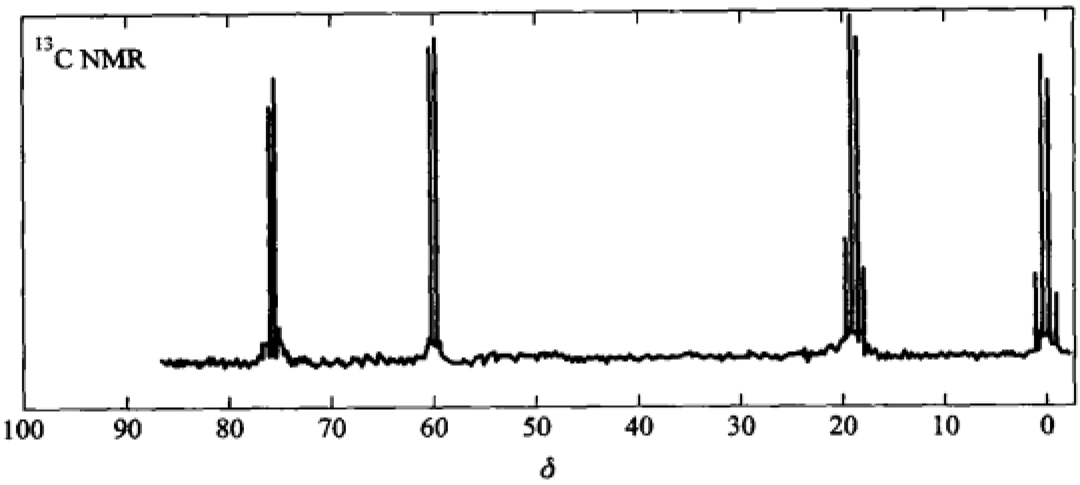
(3) Sketch the spectra expected using the DEPT-90 and DEPT-135 techniques.

(a) $CH_3—C(=O)—O—CH_2—CH_3$
ethyl acetate

(b) $H_2C=CH—CH_2Cl$
3-chloropropene

(c) 

13−15 The following off-resonance-decoupled carbon NMR was obtained from a compound of formula $C_3H_5Cl_3$. Propose a structure for this compound, and show which carbon atoms give rise to which peaks in the spectrum.



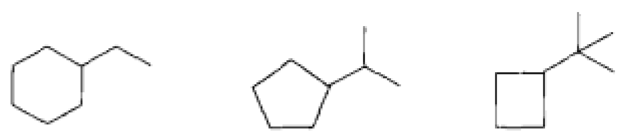
13-16 (**a**) Draw all six isomers of formula C_4H_8 (including stereoisomers).

(**b**) For each structure, show how many types of H would appear in the proton NMR spectrum.

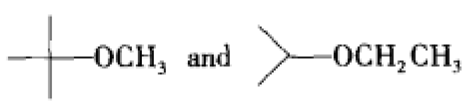
(**c**) For each structure, show how many types of C would appear in the ^{13}C NMR spectrum.

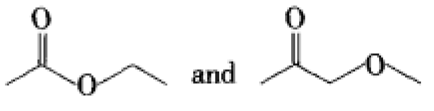
(**d**) If an unknown compound of formula C_4H_8 shows two types of H and three types of C, can you determine its structure from this information?

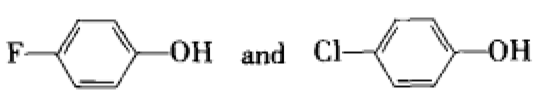
13-17 Different types of protons and carbons in alkanes tend to absorb at similar chemical shifts, making structure determination difficult. Explain how the DEPT technique would be helpful in determining which of the following isomers was in an unknown sample.



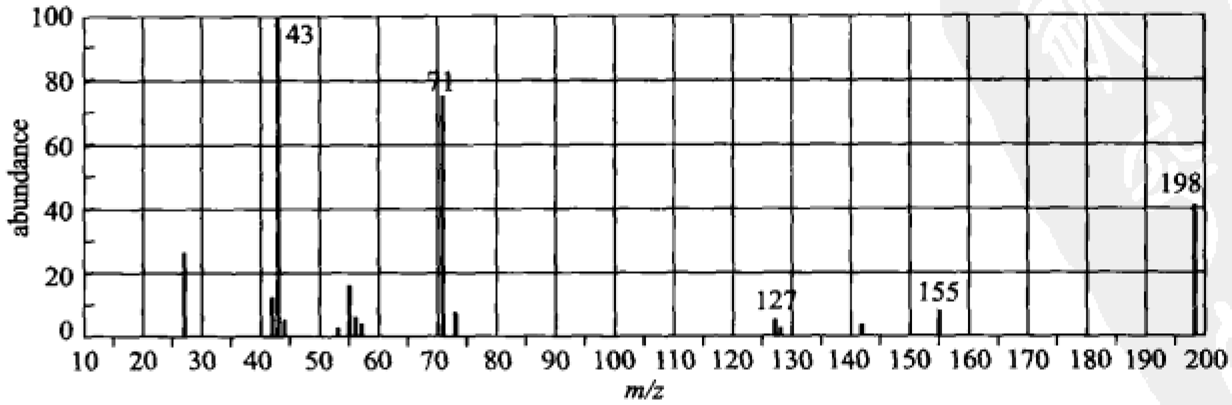
13-18 For each pair of compounds, describe which instrumental technique (IR, MS, proton NMR, carbon NMR) you could use to distinguish for certain which of the two compounds was in a sample. Describe what you would look for in each case.

(**a**) 

(**b**) 

(**c**) 

13-19 (Another true story.) A student who was checking into her lab desk found an unlabeled sample from a previous student. She was asked to identify the sample. She did an IR spectrum and declared, "It looks like an alkane." But it seemed too reactive to be an alkane, so she did a GC-MS. The mass spectrum is shown next. Identify the compound as far as you can, and state what part of your identification is uncertain. Propose fragments corresponding to the numbered peaks.

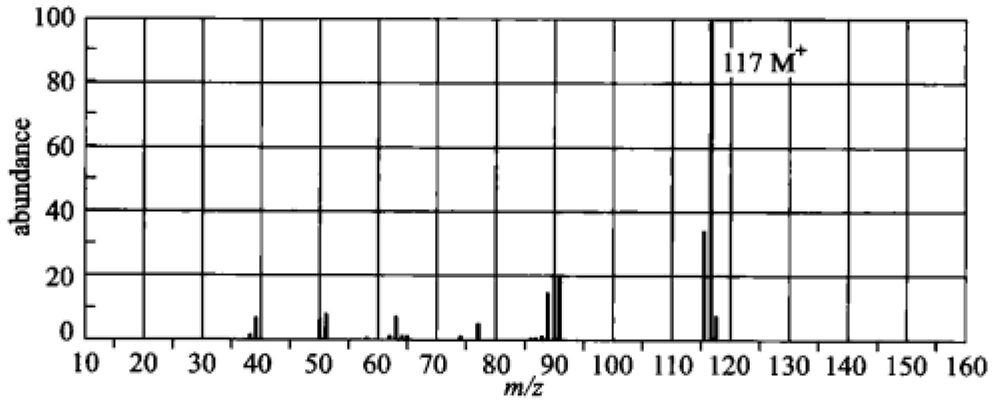


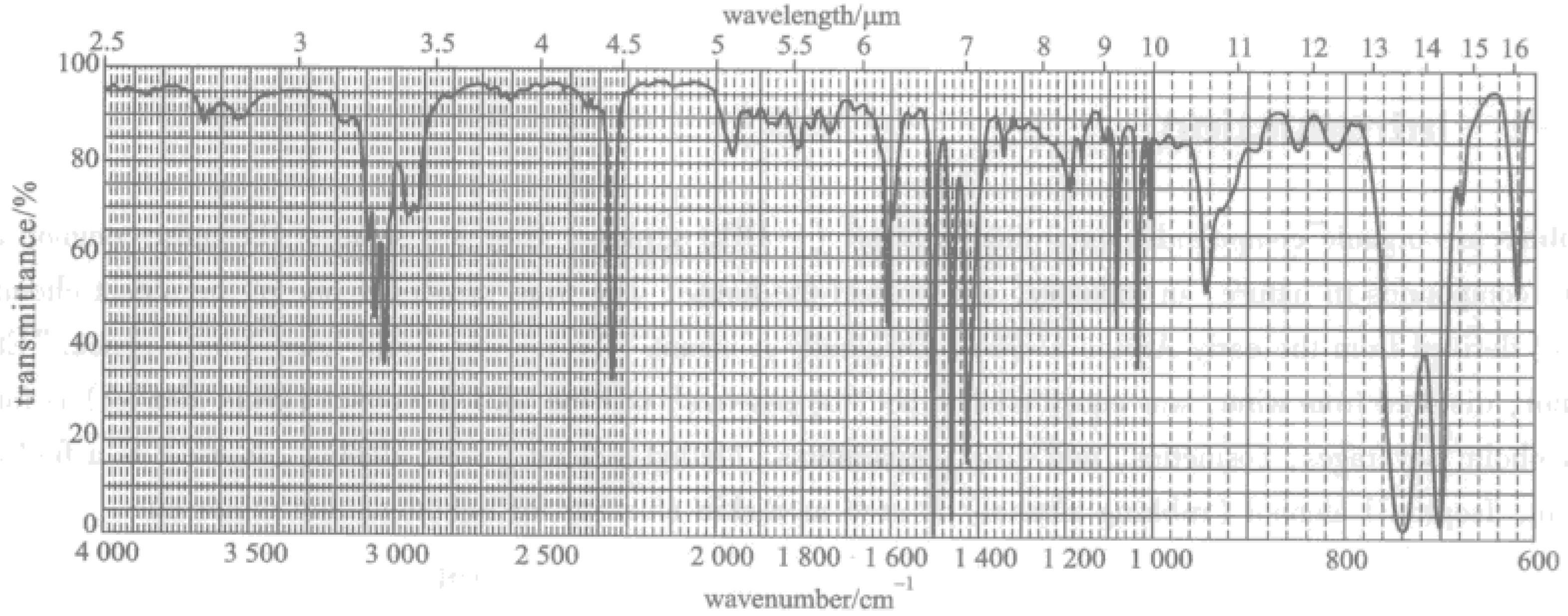
13-20 A compound was isolated as a minor constituent in an extract from garden cress. Its spectra are shown here.

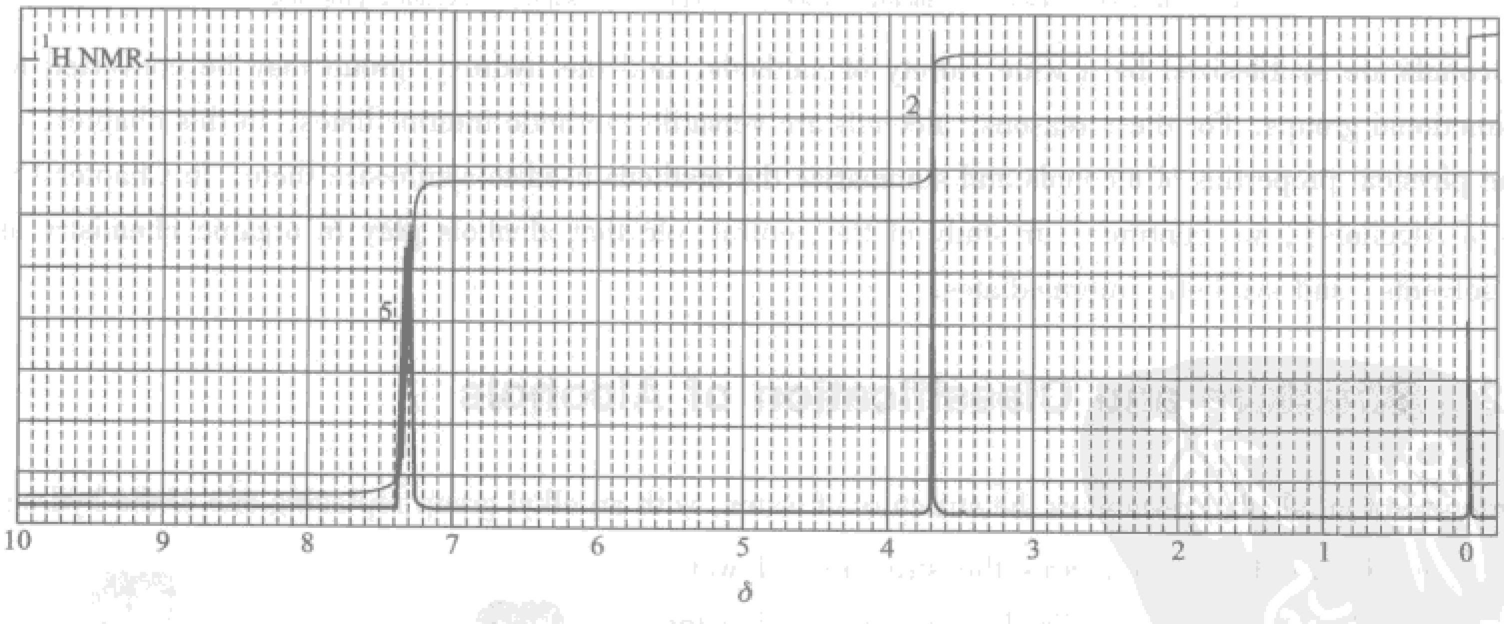
(1) Look at each spectrum individually, and list the structural characteristics you can determine from that spectrum.

(2) Look at the set of spectra as a group, and propose a tentative structure.

(3) Verify that your proposed structure accounts for the major features of each spectrum.







Chapter 14

Structure and Synthesis of Alcohols

14−1 Introduction

Alcohols are organic compounds containing hydroxyl (—OH) groups. They are some of the most common and useful compounds in nature, in industry, and around the house. The word *alcohol* is one of the oldest chemical terms, derived from the early Arabic *al-kuhl*. Originally it meant "the powder," and later "the essence." Ethyl alcohol, distilled from wine, was considered to be "the essence" of wine. Ethyl alcohol (grain alcohol) is found in alcoholic beverages, cosmetics, and drug preparations. Methyl alcohol (wood alcohol) is used as a fuel and solvent. Isopropyl alcohol (rubbing alcohol) is used as a skin cleanser for injections and minor cuts.

$CH_3—CH_2—OH$	$CH_3—OH$	$CH_3—CH(OH)—CH_3$
ethyl alcohol ethanol	methyl alcohol, methanol	isopropyl alcohol 2-propanol

Alcohols are synthesized by a wide variety of methods, and the hydroxyl group may be converted to most other functional groups. For these reasons, alcohols are versatile synthetic intermediates. In this chapter, we discuss the physical properties of alcohols and summarize the methods used to synthesize them. In Chapter 15 (Reactions of Alcohols), we continue our study of the central role that alcohols play in organic chemistry as reagents, solvents, and synthetic intermediates.

14−2 Structure and Classification of Alcohols

The structure of an alcohol resembles the structure of water, with an alkyl group replacing one of the hydrogen atoms of water. Figure 14−1 compares the structures of water and methanol. Both have sp^3-hybridized oxygen atoms, but the C—O—H bond angle in methanol (108.9°) is considerably larger than the H—O—H bond angle in water (104.5°) because the methyl group is much larger than a hydrogen atom. The bulky methyl group counteracts the bond angle compression caused by oxygen's nonbonding pairs of electrons. The O—H bond lengths are about the same in water and methanol

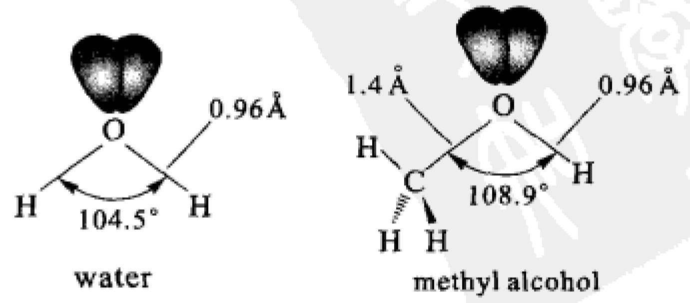


Figure 14−1 Comparison of the structures of water and methyl alcohol.

(0.96 Å), but the C—O bond is considerably longer (1.4 Å) reflecting the larger covalent radius of carbon compared to hydrogen.

One way of organizing the alcohol family is to classify each alcohol according to the type of **carbinol carbon atom**: the one bonded to the —OH group. If this carbon atom is primary (bonded to one other carbon atom), the compound is a **primary alcohol**. A **secondary alcohol** has the —OH group attached to a secondary carbon atom, and a **tertiary alcohol** has it bonded to a tertiary carbon. When we studied alkyl halides (Chapter 7), we saw that primary, secondary, and tertiary halides react differently. The same is true for alcohols. We need to learn how these classes of alcohols are similar and under what conditions they react differently. Figure 14-2 shows examples of primary, secondary, and tertiary alcohols.

Compounds with a hydroxyl group bonded directly to an aromatic (benzene) ring are called **phenols**. Phenols have many properties similar to those of alcohols, while other properties derive from their aromatic character. In this chapter, we consider the properties of phenols that are similar to those of alcohols and note some of the differences. In Chapter 17, we consider the aromatic nature of phenols and the reactions that result from that aromaticity.

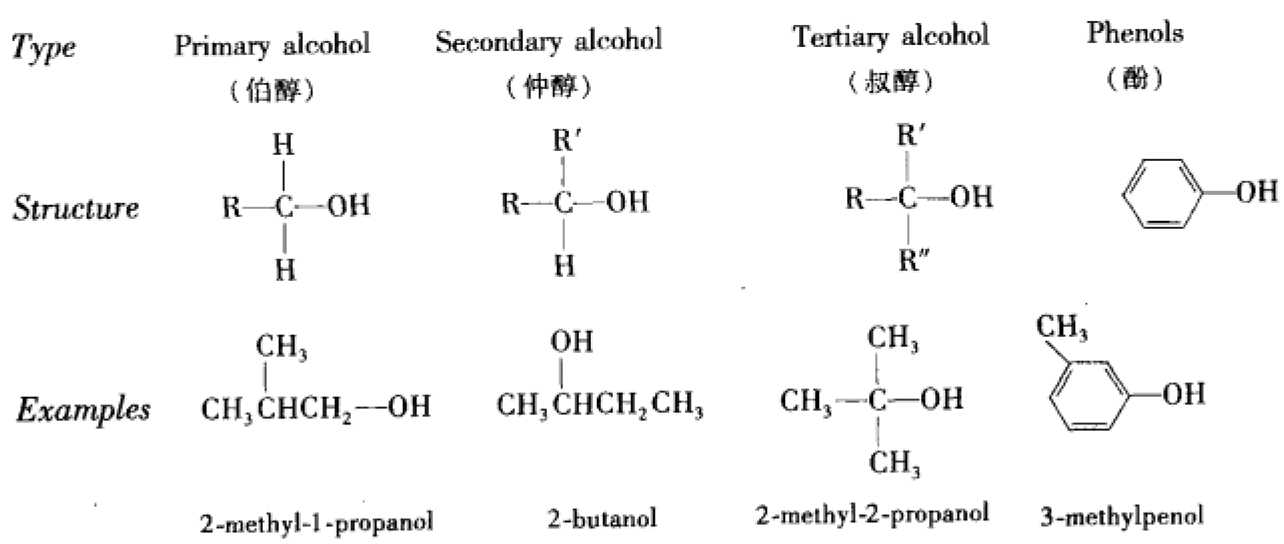


Figure 14-2 Classification of alcohols. Alcohols are classified according to the type of carbon atom (primary, secondary, or tertiary) bonded to the hydroxyl group. Phenols have a hydroxyl group bonded to a carbon atom in a benzene ring.

14-3 Physical Properties of Alcohols

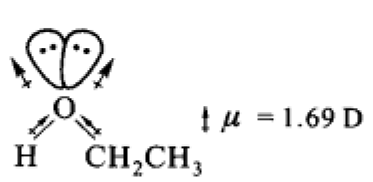
Most of the common alcohols, up to about 11 or 12 carbon atoms, are liquids at room temperature. Methanol and ethanol are free-flowing volatile liquids with characteristic fruity odors. The higher alcohols (the butanols through the decanols) are somewhat viscous, and some of the highly branched isomers are solids at room temperature. These higher alcohols have heavier but still fruity odors. 1-Propanol and 2-propanol fall in the middle, with a barely noticeable viscosity and a characteristic odor often associated with a physician's office. Table 14-1 lists the physical properties of some common alcohols.

14-3A Boiling Points of Alcohols

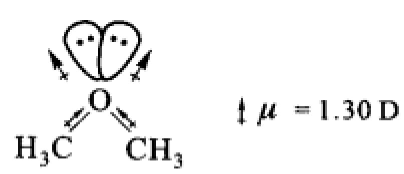
Because we often deal with liquid alcohols, we forget how surprising it *should* be that the lower molecular weight alcohols are liquids. For example, ethyl alcohol and propane have similar molecular weights, yet their boiling points differ by about 120 ℃. Dimethyl ether has an intermediate boiling point.

TABLE 14-1 Physical Properties of Selected Alcohols

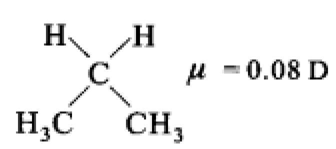
IUPAC Name	Common Name	Chinese Name	Formula	mp/℃	bp/℃	Density/ (g·mL⁻¹)
methanol	methyl alcohol	甲醇	CH_3OH	-97	65	0.79
ethanol	ethyl alcohol	乙醇	CH_3CH_2OH	-114	78	0.79
1-propanol	*n*-propyl alcohol	正丙醇	$CH_3CH_2CH_2OH$	-126	97	0.80
2-propanol	isopropyl alcohol	异丙醇	$(CH_3)_2CHOH$	-89	82	0.79
1-butanol	*n*-butyl alcohol	正丁醇	$CH_3(CH_2)_3OH$	-90	118	0.81
2-butanol	*sec*-butyl alcohol	仲丁醇	$CH_3CH(OH)CH_2CH_3$	-114	100	0.81
2-methyl-1-propanol	isobutyl alcohol	异丁醇	$(CH_3)_2CHCH_2OH$	-108	108	0.80
2-methyl-2-propanol	*t*-butyl alcohol	叔丁醇	$(CH_3)_3COH$	25	83	0.79
1-pentanol	*n*-pentyl alcohol	正戊醇	$CH_3(CH_2)_4OH$	-79	138	0.82
3-methyl-1-butanol	isopentyl alcohol	异戊醇	$(CH_3)_2CHCH_2CH_2OH$	-117	132	0.81
2,2-dimethyl-1-propanol	neopentyl alcohol	新戊醇	$(CH_3)_3CCH_2OH$	52	113	0.81
cyclopentanol	cyclopentyl alcohol	环戊醇	*cyclo*-C_5H_9OH	-19	141	0.95
1-hexanol	*n*-hexyl alcohol	正己醇	$CH_3(CH_2)_5OH$	-52	156	0.82
cyclohexanol	cyclohexyl alcohol	环己醇	*cyclo*-$C_6H_{11}OH$	25	162	0.96
1-heptanol	*n*-heptyl alcohol	正庚醇	$CH_3(CH_2)_6OH$	-34	176	0.82
1-octanol	*n*-octyl alcohol	正辛醇	$CH_3(CH_2)_7OH$	-16	194	0.83
1-nonanol	*n*-nonyl alcohol	正壬醇	$CH_3(CH_2)_8OH$	-6	214	0.83
1-decanol	*n*-decyl alcohol	正癸醇	$CH_3(CH_2)_9OH$	6	233	0.83
2-propen-1-ol	allyl alcohol	烯丙醇	$H_2C{=}CH{-}CH_2OH$	-129	97	0.86
phenylmethanol	benzyl alcohol	苄醇	$Ph{-}CH_2OH$	-15	205	1.05
diphenylmethanol	diphenylcarbinol	二苯基甲醇	Ph_2CHOH	69	298	
triphenylmethanol	triphenylcarbinol	三苯基甲醇	Ph_3COH	162	380	1.20
1,2-ethanediol	ethylene glycol	乙二醇	$HOCH_2CH_2OH$	-13	198	1.12
1,2-propanediol	propylene glycol	1,2-丙二醇	$CH_3CH(OH)CH_2OH$	-59	188	1.04
1,2,3-propanetriol	glycerol	1,2,3-丙三醇,甘油	$HOCH_2CH(OH)CH_2OH$	18	290	1.26



ethanol, MW 46
bp 78 ℃



dimethyl ether, MW 46
bp -25 ℃



propane, MW 44
bp -42 ℃

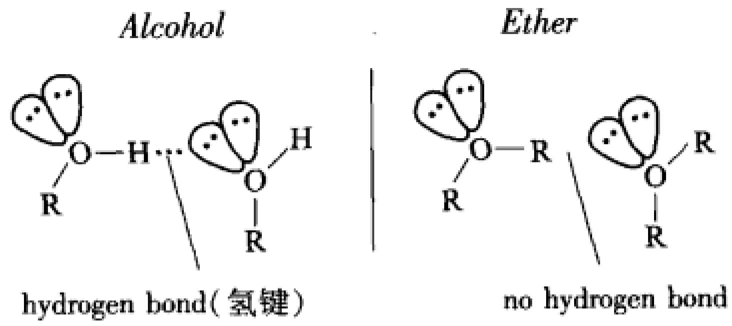
Such a large difference in boiling points suggests that ethanol molecules are attracted to each other much more strongly than propane molecules. Two important intermolecular forces are responsible: hydrogen bonding and dipole-dipole attractions.

Hydrogen bonding is the major intermolecular attraction responsible for ethanol's high boiling point. The hydroxyl hydrogen of ethanol is strongly polarized by its bond to oxygen. and it forms a hydrogen bond with a pair of nonbonding electrons from the oxygen atom of another alcohol molecule. Ethers have two alkyl groups bonded to their oxygen atoms, so they have no O—H hydrogen atoms to form hydrogen bonds. Hydrogen bonds have a strength of about 21 kJ per mole: weaker than typical covalent bonds of 300 to 500 kJ, but much stronger than dipole-dipole attractions.

Dipole-dipole attractions also contribute to the relatively high boiling points of alcohols and ethers. The polarized C—O and H—O bonds and the nonbonding electrons add to produce a dipole moment of 1.69 D in eth-

anol, compared with a dipole moment of only 0.08 D in propane. In liquid ethanol, the positive and negative ends of these dipoles align to produce attractive interactions.

We can compare the effects of hydrogen bonding and dipole-dipole attractions by comparing ethanol with dimethyl ether. Like ethanol, dimethyl ether has a large dipole moment (1.30D), but dimethyl ether cannot engage in hydrogen bonding because it has no —O—H hydrogens.



The boiling point of dimethyl ether is −25 ℃, about 17° higher than that of propane, but still 103° lower than that of ethanol. Hydrogen bonds are clearly much stronger intermolecular attractions than dipole-dipole attractions.

14-3B Solubility Properties of Alcohols

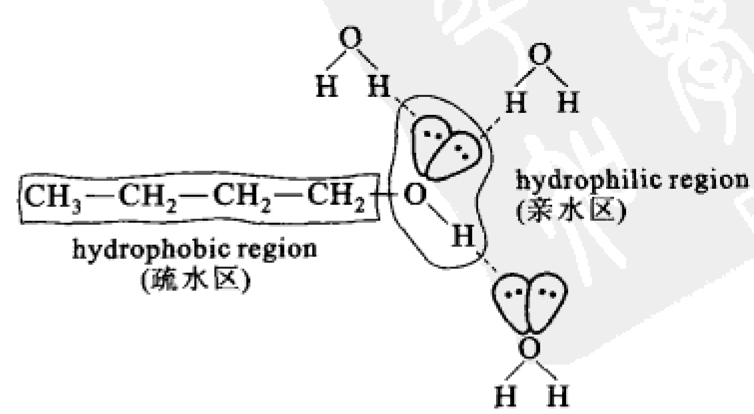
Water and alcohols have similar properties because they all contain hydroxyl groups that can form hydrogen bonds. Alcohols form hydrogen bonds with water, and several of the lower-molecular-weight alcohols are **miscible** (soluble in any proportions) with water. Similarly, alcohols are much better solvents than hydrocarbons for polar substances. Significant amounts of ionic compounds such as sodium chloride can dissolve in some of the lower alcohols. We call the hydroxyl group **hydrophilic**, meaning "water loving," because of its affinity for water and other polar substances.

The alcohol's alkyl group is called **hydrophobic** ("water hating") because it acts like an alkane: It disrupts the network of hydrogen bonds and dipole-dipole attractions of a polar solvent such as water. The alkyl group makes the alcohol less hydrophilic, yet it lends solubility in nonpolar organic solvents. As a result, many alcohols are miscible with a wide range of nonpolar organic solvents.

Table 14-2 lists the solubility of some simple alcohols in water. The water solubility decreases as the alkyl group becomes larger. Alcohols with one-, two-, or three-carbon alkyl groups are miscible with water. A four-carbon alkyl group is large enough that some isomers are not miscible, yet *t*-butyl alcohol, with a compact spherical shape, is miscible. Phenol is unusually soluble for a six-carbon alcohol because of its compact shape and the particularly strong hydrogen bonds formed between phenolic —OH groups and water molecules.

TABLE 14-2 Solubility of Alcohols in Water (at 25 ℃)

Alcohol	Solubility in Water
methyl	miscible
ethyl	miscible
n-propyl	miscible
t-butyl	miscible
isobutyl	10.0%
n-butyl	9.1%
n-pentyl	2.7%
cyclohexyl	3.6%
n-hexyl	0.6%
phenol	9.3%
hexane-1,6-diol	miscible



PROBLEM 14-1

Predict which member of each pair will be more soluble in water. Explain the reasons for your answers.

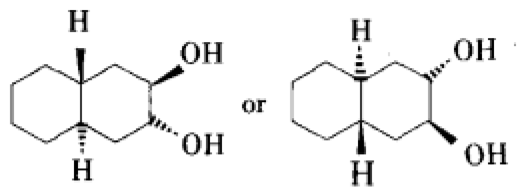
(**a**) 1-hexanol or cyclohexanol

(**b**) 1-heptanol or 4-methylphenol

(**c**) 3-ethyl-3-hexanol or 2-octanol

(**d**) 2-hexanol or cyclooctane-1,4-diol

(**e**)



PROBLEM 14-2

Dimethylamine, $(CH_3)_2NH$, has a molecular weight of 45 and a boiling point of 7.4 ℃. Trimethylamine, $(CH_3)_3N$, has a higher molecular weight (59) but a *lower* boiling point (3.5 ℃). Explain this apparent discrepancy.

14-4 Commercially Important Alcohols

Methanol (methyl alcohol) was originally produced by the destructive distillation of wood chips in the absence of air. This source led to the name **wood alcohol**. Today, most methanol is synthesized by a catalytic reaction of carbon monoxide with hydrogen. This reaction uses high temperatures and pressures and requires large, complicated industrial reactors.

$$\underset{\text{synthesis gas}}{CO + 2H_2} \xrightarrow[\text{CuO-ZnO/Al}_2\text{O}_3]{300 \text{ to } 400\ ℃,\ (200 \text{ to } 300)\times 10^5 \text{ Pa } H_2} CH_3OH$$

Synthesis gas, containing the hydrogen and carbon monoxide needed to make methanol, can be generated by the partial burning of coal in the presence of water. Careful regulation of the amount of water added allows production of synthesis gas with the correct ratio of carbon monoxide to hydrogen.

$$3C + 4H_2O \xrightarrow{\text{high temperature}} CO_2 + \underset{\text{synthesis gas(合成气)}}{2CO + 4H_2}$$

Methanol is one of the most common industrial solvents. It is cheap, relatively less toxic (compared with halogenated solvents), and it dissolves a wide variety of polar and nonpolar substances. Methanol is also a starting material for a wide variety of methyl ethers, methyl esters, and other compounds used in plastics, medicines, fuels, and solvents.

Methanol is a good fuel for internal combustion engines. Methanol is less flammable than gasoline, and water is effective against methanol fires (water mixes with and dilutes methanol). As with any alternative fuel, there are advantages and disadvantages to the use of methanol. Its high octane rating, low pollutant emissions, and lower flammability must be weighed against its lower energy content (smaller ΔH of combustion per gram), requiring 1.7 g of methanol to produce the same energy as 1 g of gasoline.

Ethanol can be produced by the fermentation of sugars and starches from many different sources. Grains such as corn, wheat, rye, and barley are common sources, resulting in the name **grain alcohol** for ethanol. Cooking the grain, followed by addition of sprouted barley, called *malt*, converts some of the starches to simpler sugars. Brewer's yeast is then added, and the solution is incubated while the yeast cells convert simple sugars such as glucose to ethanol and carbon dioxide.

$$\underset{\text{glucose(葡萄糖)}}{C_6H_{12}O_6} \xrightarrow{\text{yeast enzymes}} \underset{\text{ethanol}}{2C_2H_5OH} + 2CO_2$$

The alcoholic solution that results from fermentation contains only 12% - 15% alcohol, because yeast cells cannot survive higher concentrations. Distillation increases the alcohol concentration to about 40% -50% (80 to 100 "proof") for "hard" liquors. Distillation of ethanol-water solutions cannot increase the ethanol concentration above 95% because a solution of 95% ethanol and 5% water boils at a lower temperature (78.15 ℃) than either pure water (100 ℃) or pure ethanol (78.3 ℃). Such a mixture of liquids that boils at a lower temperature than either of its components is called a minimum-boiling **azeotrope**. When **absolute alcohol** (100% ethanol) is required, the 95% azeotrope is passed through a dehydrating agent such as anhydrous calcium oxide (CaO), which removes the final 5% of water.

Since World War II, most industrial ethanol has been synthesized directly by the catalyzed high-temperature, high-pressure, gas-phase reaction of water with ethylene. This process uses catalysts such as P_2O_5, tungsten oxide, or various specially treated clays.

$$H_2C{=}CH_2 + H_2O \xrightarrow[\text{catalyst}]{(100\ \text{to}\ 300)\times 10^5\,\text{Pa},\,300\,℃} CH_3{-}CH_2{-}OH$$

Like methanol, ethanol is an excellent solvent of low toxicity compared with truly hazardous solvents such as benzene and chloroform.

Ethanol is a good motor fuel, with similar advantages and disadvantages like methanol. Both ethanol and 2-propanol are effective topical antiseptics. Ethanol is also an ingredient in many mouthwashes. These alcohols kill the microorganisms on the wound surface and in the mouth, but their low toxicity does not kill the cells of the skin or mouth tissues.

2-Propanol (isopropyl alcohol) is made by the catalytic hydration of propylene. Isopropyl alcohol is commonly used as **rubbing alcohol** (rather than ethanol) because it has less of a drying effect on the skin. 2-Propanol is about as toxic as methanol when taken orally, but it is safer for use on the skin because it does not pass through skin as easily as methanol.

$$\underset{\text{propylene}}{CH_3{-}CH{=}CH_2} + H_2O \xrightarrow[\text{catalyst}]{(100\ \text{to}\ 300)\times 10^5\,\text{Pa},\,300\,℃} \underset{\text{2-propanol}}{CH_3{-}\underset{\substack{|\\ OH}}{CH}{-}CH_3}$$

14-5 Acidity of Alcohols and Phenols

Like the hydroxyl proton of water, the hydroxyl proton of an alcohol is weakly acidic. A strong base can remove the hydroxyl proton to give an **alkoxide ion**.

$$\underset{\text{alcohol}}{R{-}\ddot{\underset{..}{O}}{-}H} + B{:}^- \rightleftharpoons \underset{\text{alkoxide ion(烃氧离子)}}{R{-}\ddot{\underset{..}{O}}{:}^-} + B{-}H$$

Example

$$\underset{\text{ethanol}}{CH_3CH_2{-}\ddot{\underset{..}{O}}{-}H} + B{:}^- \rightleftharpoons \underset{\text{ethoxide ion(乙氧离子)}}{CH_3CH_2{-}\ddot{\underset{..}{O}}{:}^-} + B{-}H$$

The acidities of alcohols vary widely, from alcohols that are about as acidic as water to some that are much less

acidic. The acid-dissociation constant, K_a, of an alcohol is defined by the equilibrium

$$\text{R—O—H} + H_2O \overset{K_a}{\rightleftharpoons} \text{R—O}^- + H_3O^+$$

$$K_a = \frac{[H_3O^+][RO^-]}{[ROH]} \qquad pK_a = -\lg K_a$$

Table 14-3 compares the acid-dissociation constants of some alcohols with those of water and other acids.

TABLE 14-3 Acid-Dissociation Constants of Representative Alcohols

Alcohol	Structure	K_a	pK_a
methanol	CH_3—OH	3.2×10^{-16}	15.5
ethanol	CH_3CH_2—OH	1.3×10^{-16}	15.9
2-chloroethanol	Cl—CH_2CH_2—OH	5.0×10^{-15}	14.3
2,2,2-trichloroethanol	Cl_3C—CH_2—OH	6.3×10^{-13}	12.2
isopropyl alcohol	$(CH_3)_2CH$—OH	3.2×10^{-17}	16.5
t-butyl alcohol	$(CH_3)_3C$—OH	1.0×10^{-18}	18.0
cyclohexanol	C_6H_{11}—OH	1.0×10^{-18}	18.0
phenol(苯酚)	C_6H_5—OH	1.0×10^{-10}	10.0
	Comparison with Other Acids		
water	H_2O	1.8×10^{-16}	15.7
acetic acid (乙酸)	CH_3COOH	1.6×10^{-5}	4.8
hydrochloric acid (氢氯酸,盐酸)	HCl	1.6×10^{2}	-2.2

14-5A Effects on Acidity

The acid-dissociation constants for alcohols vary according to their structure, from about 10^{-16} for methanol down to about 10^{-18} for most tertiary alcohols. The acidity decreases as the substitution on the alkyl group increases, because a more highly substituted alkyl group inhibits solvation of the alkoxide ion and drives the dissociation equilibrium to the left.

Table 14-3 shows that substitution by electron-withdrawing halogen atoms enhances the acidity of alcohols. For example, 2-chloroethanol is more acidic than ethanol because the electron-withdrawing chlorine atom helps to stabilize the 2-chloroethoxide ion.

$$\underset{\text{ethanol}}{CH_3\text{—}CH_2\text{—}OH} + H_2O \rightleftharpoons \underset{\text{ethoxide ion (less stable)}}{CH_3\text{—}CH_2\text{—}O^-} + H_3O^+ \qquad K_a = 1.3\times10^{-16}$$

$$\underset{\text{2-chloroethanol}}{Cl\text{—}CH_2\text{—}CH_2\text{—}OH} + H_2O \rightleftharpoons Cl\text{—}CH_2\text{—}CH_2\text{—}O^- + H_3O^+ \qquad K_a = 5.0\times10^{-15}$$

2-chloroethoxide ion(2-氯乙氧负离子)
(stabilized by Cl)

PROBLEM 14-3

Predict which member of each pair will be more acidic. Explain your answers.

(a) methanol or *t*-butyl alcohol
(b) 2-chloropropan-1-ol or 3-chloropropan-1-ol
(c) 2-chloroethanol or 2, 2-dichloroethanol
(d) 2,2-dichloropropan-1-ol or 2,2-difluoropropan-1-ol

PROBLEM 14-4

Without looking them up, rank the following compounds in decreasing order of acidity. These examples represent large classes of compounds that differ widely in acidity.

water, ethanol, 2-chloroethanol, *t*-butyl alcohol, ammonia, sulfuric acid, hexane

14-5B Formation of Sodium and Potassium Alkoxides

In Chapter 15, we will see many useful reactions of alkoxide ions. When an alkoxide ion is needed in a synthesis, it is often formed by the reaction of sodium or potassium metal with the alcohol. This is an oxidation-reduction, with the metal being oxidized and the hydrogen ion reduced to form hydrogen gas. Hydrogen bubbles out of the solution, leaving the sodium or potassium salt of the alkoxide ion.

$$\text{R—O—H} + \text{Na} \longrightarrow \text{R—O}^{-}\,{}^{+}\text{Na} + \frac{1}{2}\text{H}_2\uparrow$$

Example

$$\underset{\text{ethanol}}{CH_3CH_2OH} + \underset{\text{sodium metal}}{Na} \longrightarrow \underset{\text{sodium ethoxide(乙醇钠)}}{CH_3CH_2O^{-}\,{}^{+}Na} + \underset{\text{hydrogen gas}}{\frac{1}{2}H_2\uparrow}$$

The more acidic alcohols, like methanol and ethanol, react rapidly with sodium to form sodium methoxide and sodium ethoxide. Secondary alcohols, such as 2-propanol, react more slowly. Tertiary alcohols, such as *t*-butyl alcohol, react very slowly with sodium. Potassium is often used with secondary and tertiary alcohols because it is more reactive than sodium, and the reaction can be completed in a convenient amount of time.

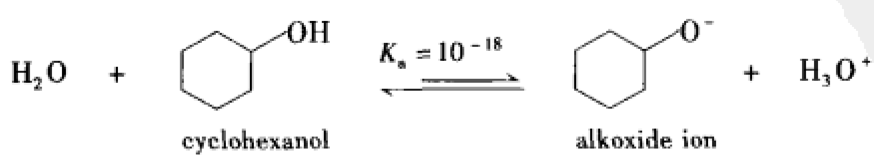
$$\underset{t\text{-butyl alcohol}}{(CH_3)_3C\text{—}OH} + \underset{\text{potassium metal}}{K} \longrightarrow \underset{\text{potassium } t\text{-butoxide(叔丁醇钾)}}{(CH_3)_3C\text{—}O^{-}\,{}^{+}K} + \frac{1}{2}H_2\uparrow$$

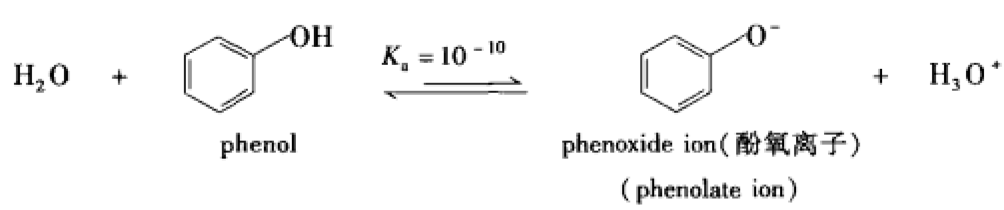
Some alcohols react slowly with both sodium and potassium. In these cases, a useful alternative is sodium hydride, often in tetrahydrofuran (THF) solution. Sodium hydride reacts quickly to form the alkoxide, even with difficult compounds.

$$\underset{\text{alcohol}}{\text{R—}\ddot{\underset{\cdot\cdot}{O}}\text{—H}} + \underset{\text{sodium hydride (氢化钠)}}{NaH} \xrightarrow{\text{THF(四氢呋喃)}} \underset{\text{sodium alkoxide(醇钠)}}{\text{R—}\ddot{\underset{\cdot\cdot}{O}}\text{:}^{-}\,{}^{+}Na} + \underset{\text{hydrogen}}{H_2\uparrow}$$

14-5C Acidity of Phenols

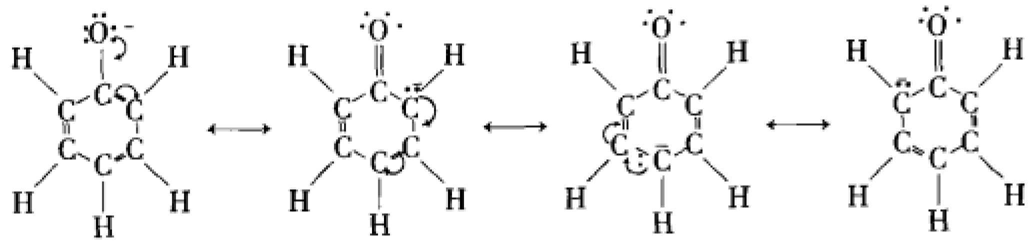
We might expect that phenol would have about the same acidity as cyclohexanol, since their structures are similar. This prediction is wrong: Phenol is nearly 100 million (10^8) times more acidic than cyclohexanol.





Cyclohexanol is a typical secondary alcohol, with a typical acid-dissociation constant. There must be something

special about phenol that makes it unusually acidic. The phenoxide ion is more stable than a typical alkoxide ion because the negative charge is not confined to the oxygen atom but is delocalized over the oxygen and three carbon atoms of the ring.



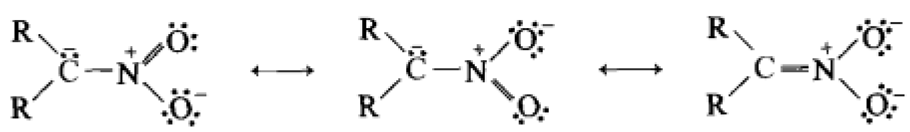
A large part of the negative charge in the resonance hybrid still resides on the oxygen atom, since it is the most electronegative of the four atoms sharing the charge. But the ability to spread the negative charge over four atoms rather than concentrating it on just one atom produces a more stable ion. The reaction of phenol with sodium hydroxide is exothermic, and the following equilibrium lies to the right.

phenol, $pK_a = 10.0$ sodium phenoxide (苯酚钠) $pK_a = 15.7$

Phenoxide anions are prepared simply by adding the phenol to an aqueous solution of sodium hydroxide or potassium hydroxide. There is no need to use sodium or potassium metal. Phenol was once called *carbolic acid* because of its ability to neutralize common bases.

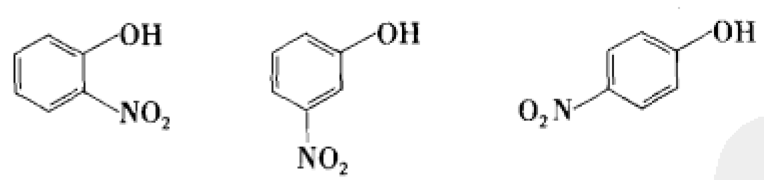
PROBLEM 14-5

Anitro group ($—NO_2$) effectively stabilizes a negative charge on an adjacent carbon atom through resonance:



minor minor major

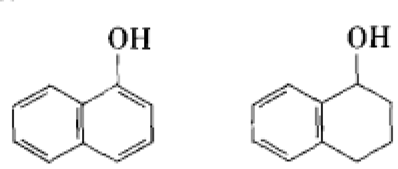
Two of the following nitrophenols are much more acidic than phenol itself. The third compound is only slightly more acidic than phenol. Use resonance structures of the appropriate phenoxide ions to show why two of these anions should be unusually stable.



2-nitrophenol 3-nitrophenol 4-nitrophenol

PROBLEM 14-6

The following compounds are only slightly soluble in water, but one of them is very soluble in a dilute aqueous solution of sodium hydroxide. The other is still only slightly soluble.



(a) Explain the difference in solubility of these compounds in dilute sodium hydroxide.

(b) Show how this difference might be exploited to separate a mixture of these two compounds using a separatory funnel.

14-6 Organometallic Reagents for Alcohol Synthesis

Organometallic compounds contain covalent bonds between carbon atoms and metal atoms. Organometallic reagents are useful because they have nucleophilic carbon atoms, in contrast to the electrophilic carbon atoms of alkyl halides. Most metals (M) are more electropositive than carbon, and th C—M bond is polarized with a partial positive charge on the metal and a partial negative charge on carbon. The following partial periodic table shows the electronegativities of some metals used in making organometallic compounds.

Electronegativities

Li	1.0					C	2.5
Na	0.9	Mg	1.3	Al	1.6		
K	0.8						

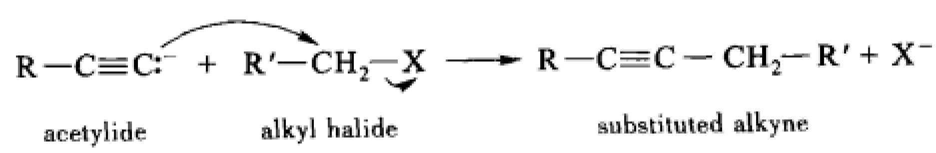
C—M bond

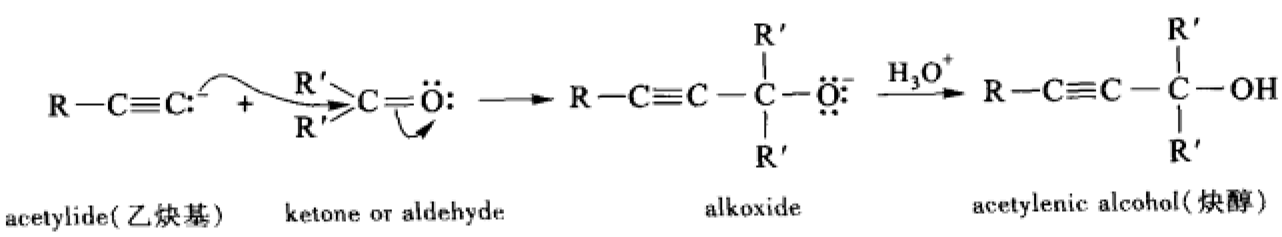
$\overset{\delta^-}{C} \rightleftharpoons \overset{\delta^+}{Li}$

$\overset{\delta^-}{C} \rightleftharpoons \overset{\delta^+}{Mg}$

We have already encountered one type of organometallic compound with a negative charge on carbon: sodium acetylides, covered in Section 10-6. Terminal alkynes are weakly acidic, and they are converted to sodium acetylides by treatment with an unusually strong base, sodium amide. These sodium acetylides are useful nucleophiles, reacting with alkyl halides and carbonyl compounds to form new carbon-carbon bonds.

$$\underset{\text{terminal alkyne(端炔)}}{R—C\equiv C—H} + \underset{\text{sodium amide(氨基钠)}}{NaNH_2} \longrightarrow \underset{\text{a sodium acetylide(乙炔钠)}}{R—C\equiv C\!:^{-}\,Na^{+}} + \underset{\text{ammonia}}{NH_3}$$





Most alkyl and alkenyl groups are not acidic enough to be deprotonated by sodium amide, but they can be made into Grignard reagents and organolithium reagents. These reagents are extremely versatile, providing some of our best ways of forming carbon-carbon bonds.

14-6A Grignard Reagents

Organometallic compounds of lithium and magnesium are most frequently used for the synthesis of alcohols. The organomagnesium halides, of empirical formula R—Mg—X, are called **Grignard reagents** in honor of the French chemist Victor Grignard, who discovered their utility around 1905 and received the Nobel Prize in chemistry in 1912. Grignard reagents result from the reaction of an alkyl halide with magnesium metal. This reaction is always carried out in an ether solvent, which is needed to solvate and stabilize the Grignard reagent as it forms. Although we write the Grignard reagent as R—Mg—X, the actual species in solution usually contains two, three, or four of these units associated together with several molecules of the ether solvent. Diethyl ether, $CH_3CH_2—O—CH_2CH_3$, is the most common solvent for these reactions, although other ethers are also used.

$$\underset{(X = Cl, Br, \text{or } I)}{R—X} + Mg \xrightarrow{CH_3CH_2OCH_2CH_3} \underset{\substack{\text{organomagnesium halide(有机镁卤化物)}\\ \text{(Grignard reagent)}}}{\overset{\delta^-}{R}—\overset{\delta^+}{Mg}—X} \qquad \text{reacts like } R\!:^{-}\ \overset{+}{Mg}X$$

Grignard reagents may be made from primary, secondary, and tertiary alkyl halides, as well as from vinyl and aryl halides. Alkyl iodides are the most reactive halides, followed by bromides and chlorides. Alkyl fluorides generally do not react.

$$\text{reactivity: } R{-}I > R{-}Br > R{-}Cl \gg R{-}F$$

The following reactions show the formation of some typical Grignard reagents.

$$\underset{\text{iodomethane}}{CH_3{-}I} + Mg \xrightarrow{\text{ether}} \underset{\text{methylmagnesium iodide(碘化甲基镁)}}{CH_3{-}Mg{-}I}$$

bromocyclohexane cyclohexylmagnesium bromide(溴化环己基镁)

$$\underset{\text{allyl bromide(烯丙基溴)}}{H_2C{=}CH{-}CH_2{-}Br} + Mg \xrightarrow{\text{ether}} \underset{\text{allylmagnesium bromide(溴化烯丙基镁)}}{H_2C{=}CH{-}CH_2{-}MgBr}$$

14-6B Organolithium Reagents

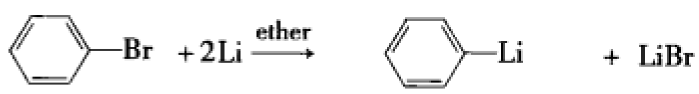
Like magnesium, lithium reacts with alkyl halides, vinyl halides, and aryl halides to form organometallic compounds. Ether is not necessary for this reaction. **Organolithium reagents** are made and used in a wide variety of solvents, including alkanes.

$$\underset{(X = Cl,\ Br,\ \text{or } I)}{R{-}X + 2Li} \longrightarrow Li^{+\,-}X + \underset{\text{organolithium(有机锂)}}{R{-}Li} \quad \text{reacts like } R\!:^{-}\,Li^{+}$$

Examples

$$\underset{n\text{-butyl bromide}}{CH_3CH_2CH_2CH_2{-}Br} + 2Li \xrightarrow{\text{hexane}} \underset{n\text{-butyllithium(丁基锂)}}{CH_3CH_2CH_2CH_2{-}Li} + LiBr$$

$$\underset{\text{vinyl chloride}}{H_2C{=}CH{-}Cl} + 2Li \xrightarrow{\text{pentane}} \underset{\text{vinyllithium(乙烯基锂)}}{H_2C{=}CH{-}Li} + LiCl$$



bromobenzene phenyllithium(苯基锂)

PROBLEM 14-7

Which of the following compounds are suitable solvents for Grignard reactions?

(a) n-hexane

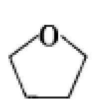
(b) $CH_3{-}O{-}CH_3$

(c) $CHCl_3$

(d) cyclohexane

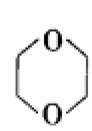
(e) benzene

(f) $CH_3OCH_2CH_2OCH_3$

(g) 

THF

(tetrahydrofuran, 四氢呋喃)

(h) 

1,4-dioxane(1,4-二噁烷)

PROBLEM 14−8

Predict the products of the following reactions.

(**a**) $CH_3CH_2Br \quad + \quad Mg \xrightarrow{\text{ether}}$

(**b**) isobutyl iodide $\quad + \quad Li \xrightarrow{\text{hexane}}$

(**c**) 1-bromo-4-fluorocyclohexane $\quad + \quad Mg \xrightarrow{\text{THF}}$

(**d**) $CH_2 = CCl—CH_2CH_3 \quad + \quad Li \xrightarrow{\text{ether}}$

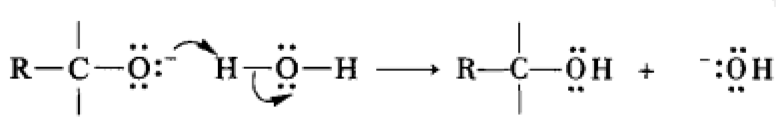
14−7 Synthesis of Alcohols: Addition of Organometallic Reagents to Carbonyl Compounds

One of the reasons alcohols are important synthetic intermediates is that they can be synthesized directly from a wide variety of other functional groups. In Chapters 7 and 9, we examined the conversion of alkyl halides to alcohols by substitution and the conversion of alkenes to alcohols by hydration, hydroboration, and hydroxylation. In this chapter, we will consider the largest and most versatile group of alcohols synthesis: nucleophilic additions to carbonyl compounds.

14−7A Addition of Organometallic Reagents to Carbonyl Groups of Aldehydes and Ketones

Because they resemble carbanions, Grignard and organolithium reagents are strong nucleophiles and strong bases. Their most useful nucleophilic reactions are additions to carbonyl (C =O) groups, much like we saw with acetylide ions (Section 10−6B). The carbonyl group is polarized, with a partial positive charge on carbon and a partial negative charge on oxygen. The positively charged carbon is electrophilic; attack by a nucleophile places a negative charge on the electronegative oxygen atom.

The product of this nucleophilic attack is an alkoxide ion, a strong base. Addition of water or a dilute acid protonates the alkoxide to give the alcohol.



alkoxide (or H_3O^+)

Either a Grignard reagent or an organolithium reagent can serve as the nucleophile in this addition to a carbonyl group. We are interested primarily in the reactions of Grignard reagents with ketones and aldehydes. The following discussions refer to Grignard reagents, but they also apply to organolithium reagents. The Grignard reagent adds to the carbonyl group to form an alkoxide ion. Addition of dilute acid (in a separate step) protonates the alkoxide to give the alcohol.

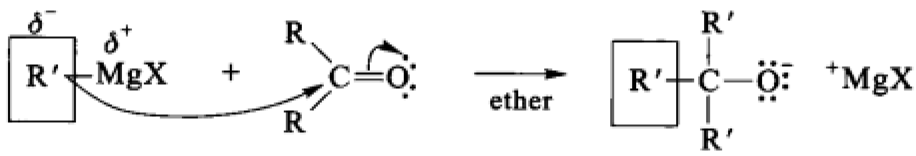
KEY MECHANISM 14-1 Grignard Reactions

Grignard and organolithium reagents provide some of the best methods for assembling a carbon skeleton. These strong nucleophiles add to ketones and aldehydes to give alkoxide ions, which are protonated to give alcohols.

***Formation of the Grignard reagent*:** Magnesium reacts with an alkyl halide in an ether solution.

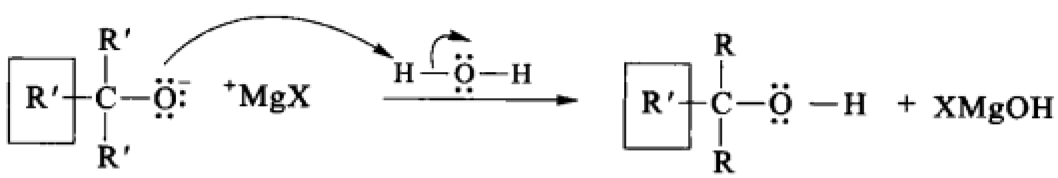
$$R'\text{—}X \quad + \quad Mg \xrightarrow[\text{ether}]{} R'\text{—}MgX$$

***Reaction 1*:** The Grignard reagent attacks a carbonyl compound to form an alkoxide salt.



magnesium alkoxide salt(烷氧基镁盐)

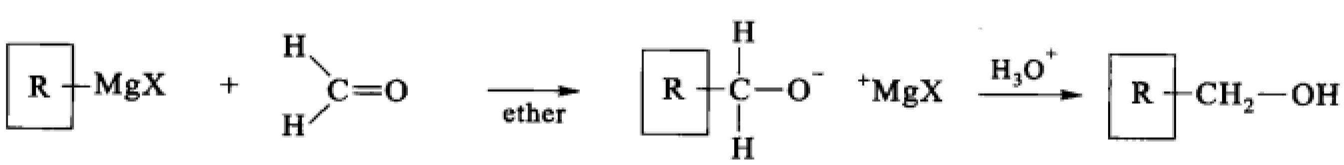
***Reaction 2*:** After the first reaction is complete, water or dilute acid is added to protonate the alkoxide and give the alcohol.



magnesium alkoxide salt alcohol

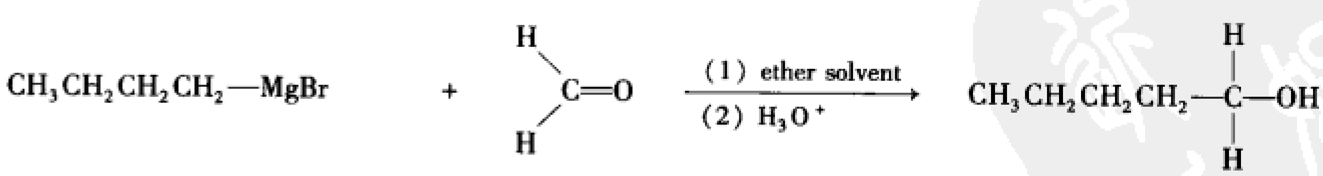
QUESTION: What would be the result if water were accidentally added in the first reaction with the Grignard reagent and the carbonyl compound?

Formation of Primary Alcohols Addition of a Grignard reagent to formaldehyde, followed by protonation, gives a primary alcohol with one more carbon atom than in the Grignard reagent.



Grignard reagent formaldehyde(甲醛) primary alcohol(伯醇)

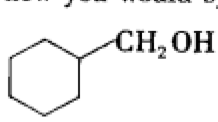
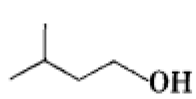
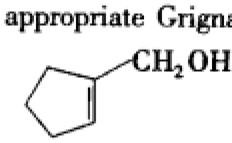
For example,



butylmagnesium bromide(溴化丁基镁) formaldehyde 1-pentanol(92%)

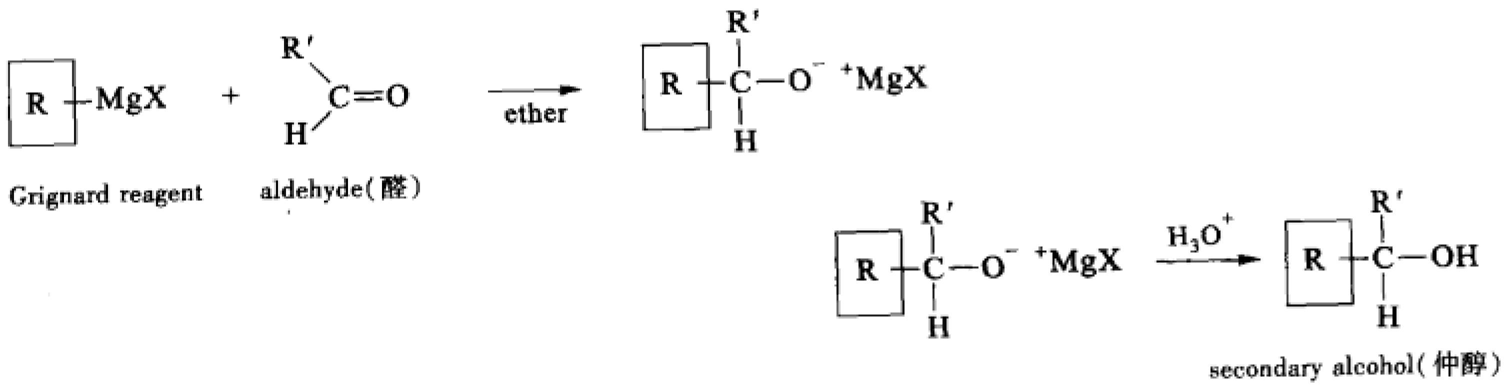
PROBLEM 14-9

Show how you would synthesize the following alcohols by adding an appropriate Grignard reagent to formaldehyde.

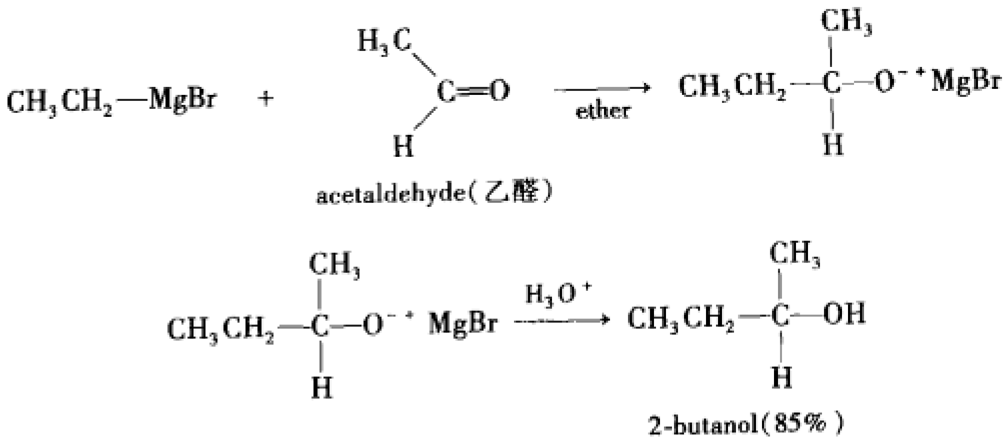
(a)  (b)  (c) 

Formation of Secondary Alcohols Grignard reagents add to aldehydes to give, after protonation, secondary

alcohols.

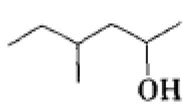
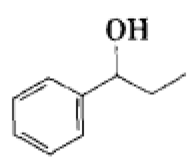
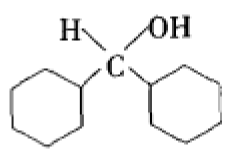


The two alkyl groups of the secondary alcohol are the alkyl group from the Grignard reagent and the alkyl group that was bonded to the carbonyl group of the aldehyde.

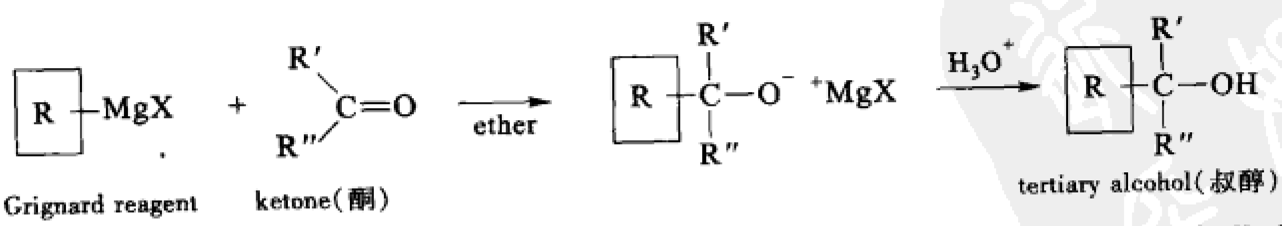


PROBLEM 14-10

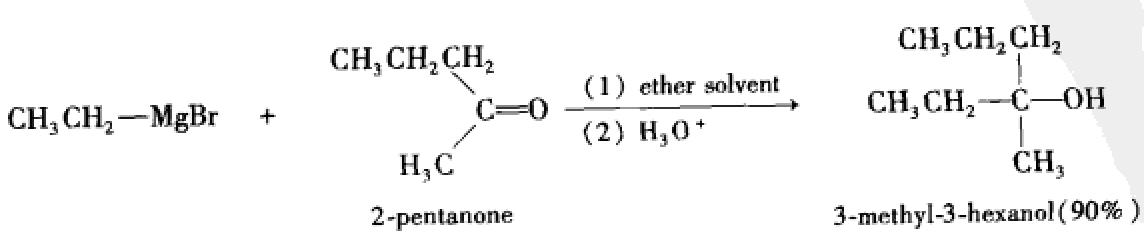
Show two ways you could synthesize each of the following alcohols by adding an appropriate Grignard reagent to an aldehyde.

(a)  (b)  (c) 

Formation of Tertiary Alcohols A ketone has two alkyl groups bonded to its carbonyl carbon atom. Addition of a Grignard reagent, followed by protonation, gives a tertiary alcohol, with three alkyl groups bonded to the carbinol carbon atom.



Two of the alkyl groups are the two originally bonded to the ketone carbonyl group. The third alkyl group comes from the Grignard reagent.



PROBLEM 14-11

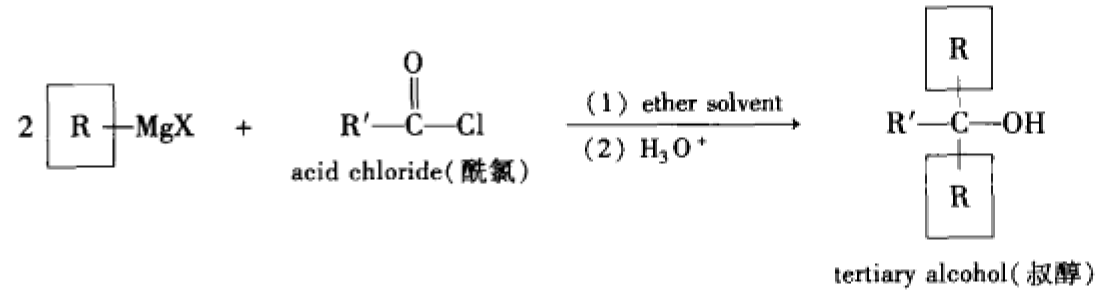
Show how you would synthesize each alcohol by adding an appropriate Grignard reagent to a ketone.

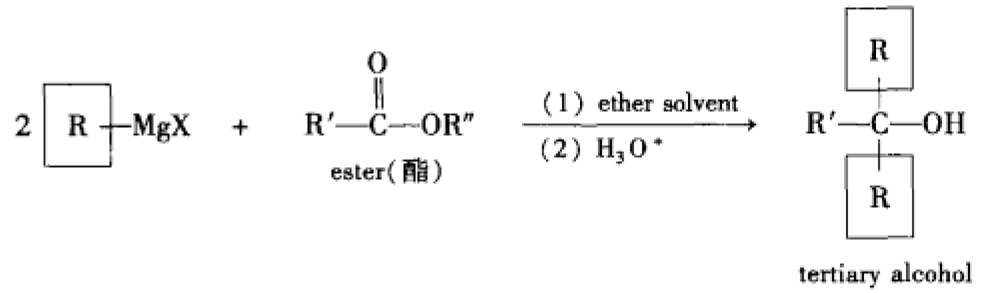
(a) 3-phenylhexan-3-ol (3 ways) (b) Ph_3COH

(c) 1-methylcyclohexanol (d) 1,1-dicyclohexyl-1-butanol

14-7B Addition of Grignard Reagents to Carbonyl Groups of Acid Chlorides and Esters

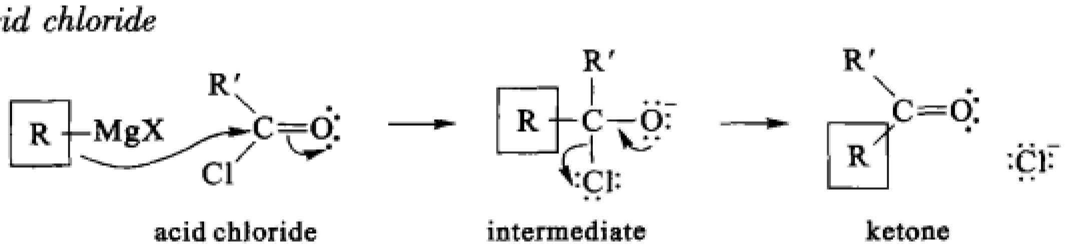
Acid chlorides and esters react with two equivalents of Grignard reagents to give (after protonation) tertiary alcohols.



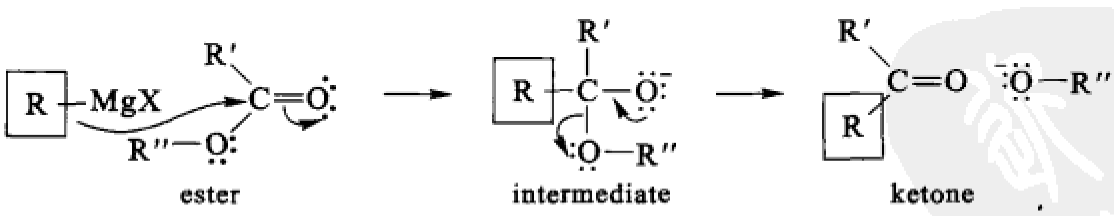


Addition of the first equivalent of the Grignard reagent produces an unstable intermediate that expels a chloride ion (in the acid chloride) or an alkoxide ion (in the ester), to give a ketone. The alkoxide ion is a suitable leaving group in this reaction because its leaving stabilizes a negatively charged intermediate in a strongly exothermic step.

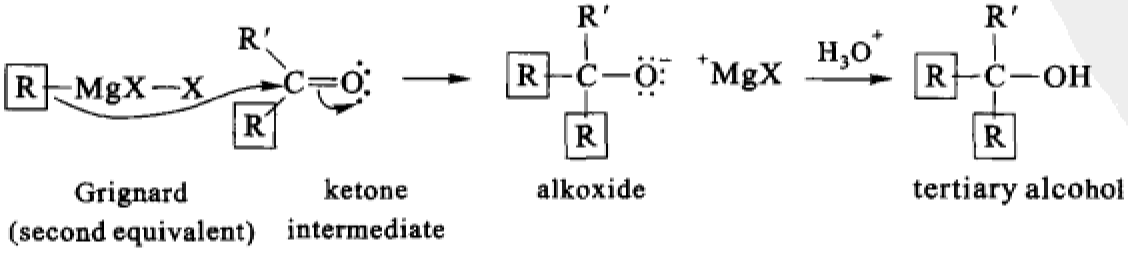
Attack on an acid chloride



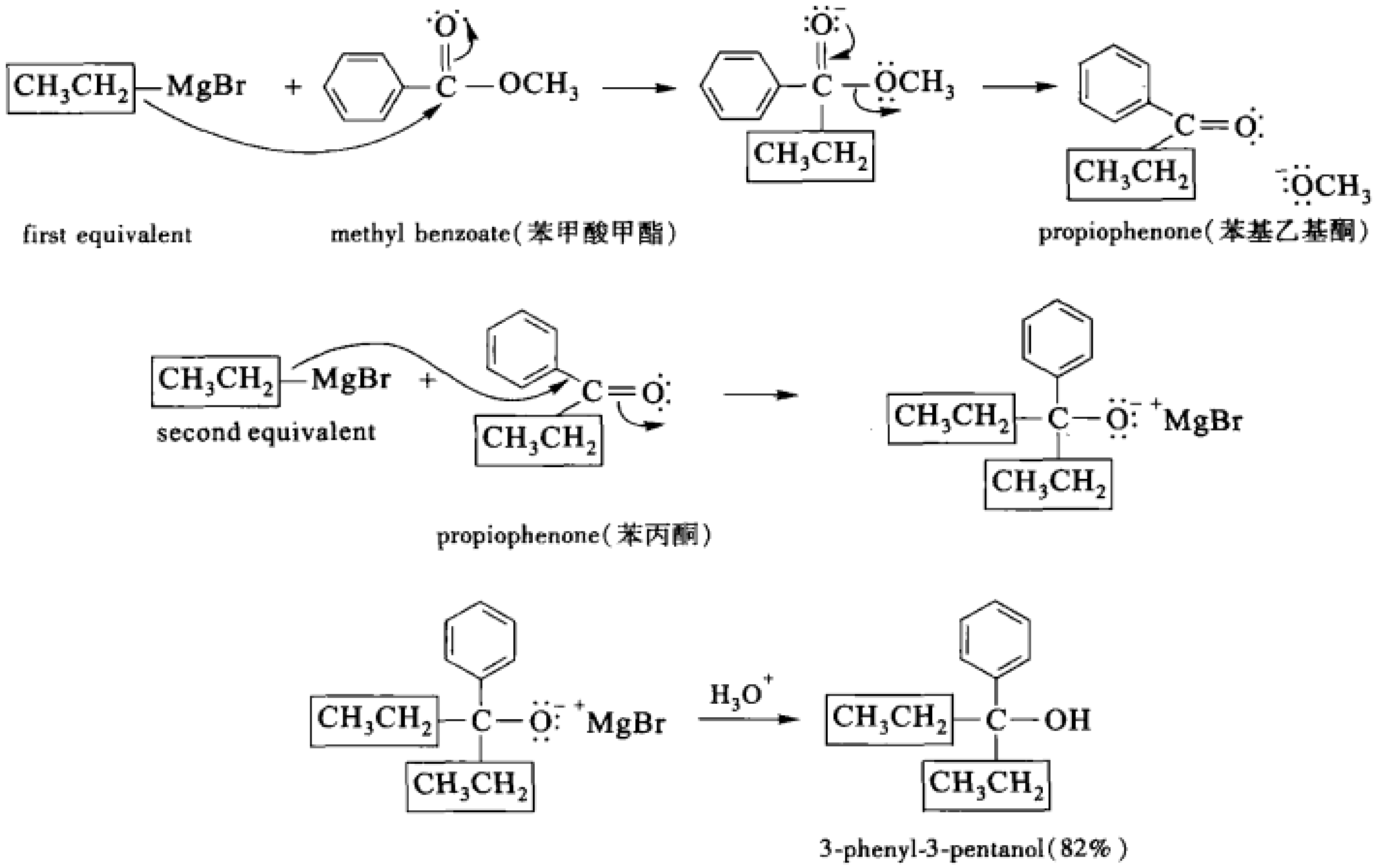
Attack on an ester



The ketone reacts with a second equivalent of the Grignard reagent, forming the magnesium salt of a tertiary alkoxide. Protonation gives a tertiary alcohol with one of its alkyl groups derived from the acid chloride or ester, and the other two derived from the Grignard reagent.

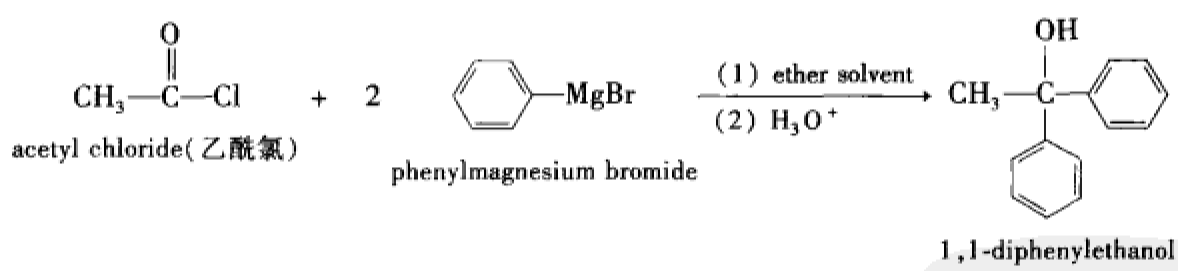


Consider an example using an ester. When an excess of ethylmagnesium bromide is added to methyl benzoate, the first equivalent adds and methoxide is expelled, giving propiophenone. Addition of a second equivalent, followed by protonation, gives a tertiary alcohol: 3-phenyl-3-pentanol.



PROBLEM 14-12

Propose a mechanism for the reaction of acetyl chloride with phenylmagnesium bromide to give 1, 1-diphenylethanol.



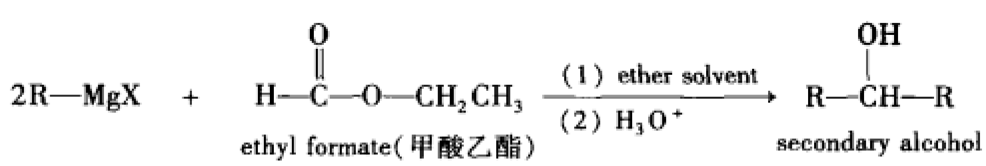
PROBLEM 14-13

Show how you would add Grignard reagents to acid chlorides or esters to synthesize the following alcohols.

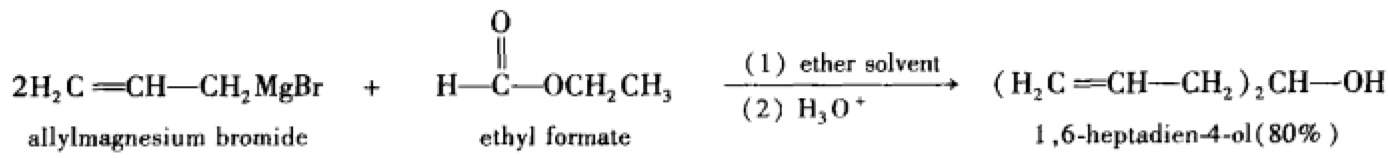
(a) Ph_3C—OH (b) 3-ethyl-2-methyl-3-pentanol (c) dicyclohexylphenylmethanol

PROBLEM 14-14

A formate ester, such as ethyl formate, reacts with an excess of a Grignard reagent to give (after protonation) secondary alcohols with two identical alkyl groups.



(a) Propose a mechanism to show how the reaction of ethyl formate with an excess of allylmagnesium bromide gives, after protonation, 1,6-heptadien-4-ol.

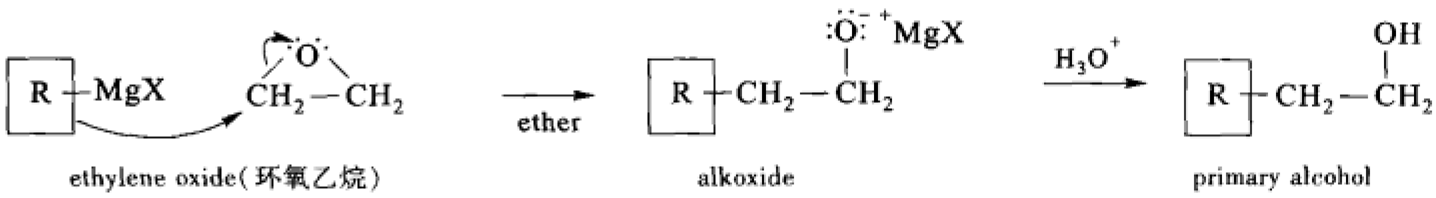


(b) Show how you would use reactions of Grignard reagents with ethyl formate to synthesize the following secondary alcohols.

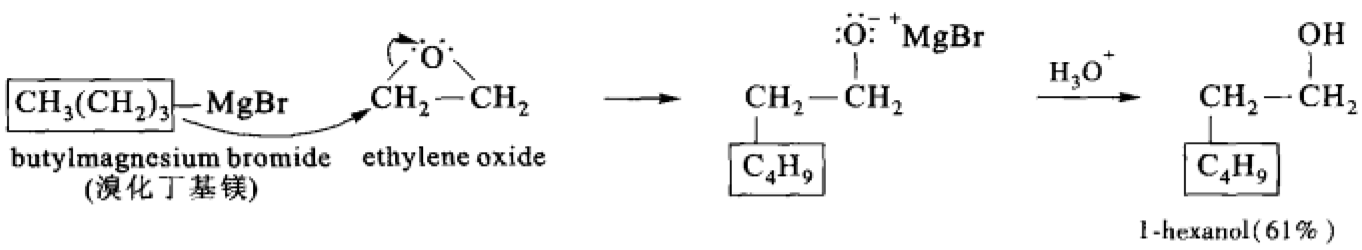
(i) 3-pentanol **(ii)** diphenylmethanol **(iii)** *trans*, *trans*-2,7-nonadien-5-ol

14-7C Addition of Grignard Reagents to Ethylene Oxide

Grignard reagents usually do not react with ethers, but **epoxides** are unusually reactive ethers because of their ring strain. Ethylene oxide reacts with Grignard reagents to give, after protonation, primary alcohols with *two* additional carbon atoms. Notice that the nucleophilic attack by the Grignard reagent opens the ring and relieves the ring strain.



Example

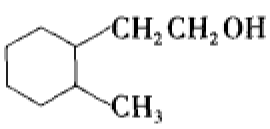


PROBLEM 14-15

Show how you would synthesize the following alcohols by adding Grignard reagents to ethylene oxide.

(a) 2-phenylethanol **(b)** 4-methyl-1-pentanol

(c)

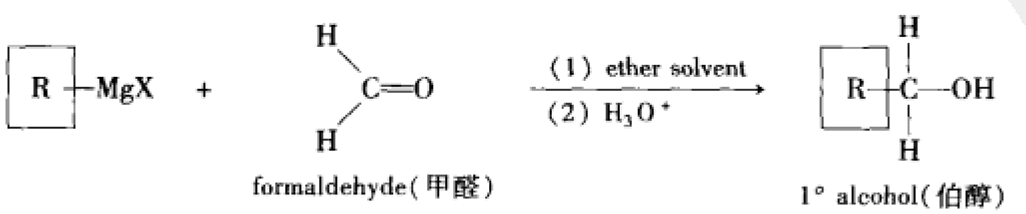


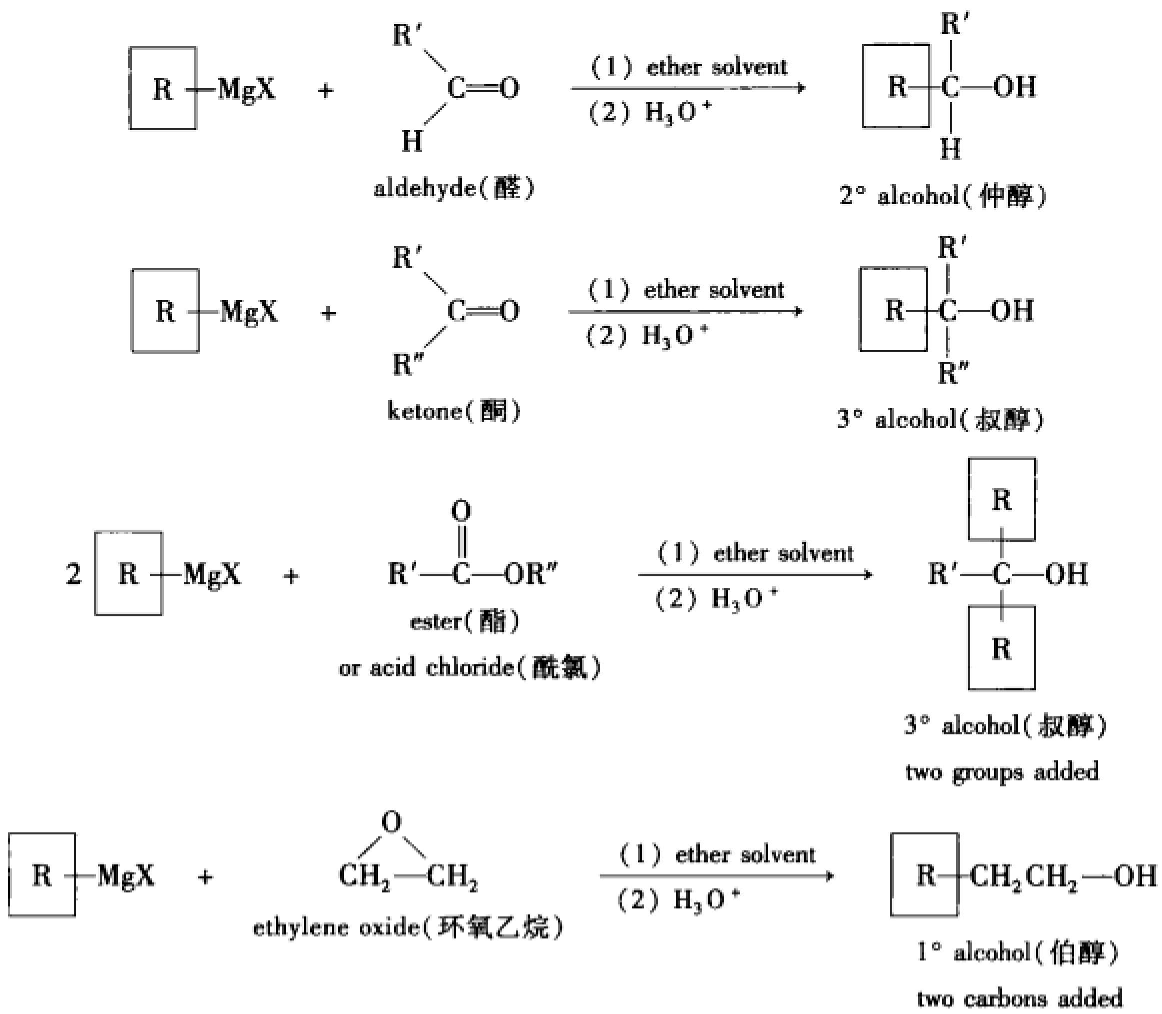
PROBLEM 14-16

In Section 10-6B, we saw how acetylide ions add to carbonyl groups in much the same way that Grignard and organolithium reagents add. Acetylide ions also add to ethylene oxide much like Grignard and organolithium reagents. Predict the products obtained by adding the following acetylide ions to ethylene oxide, followed by a dilute acid workup.

(a) $HC\equiv C:^-$ **(b)** $CH_3CH_2-C\equiv C:^-$

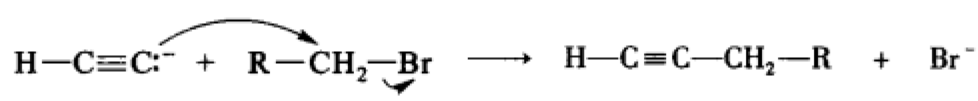
SUMMARY Grignard Reactions



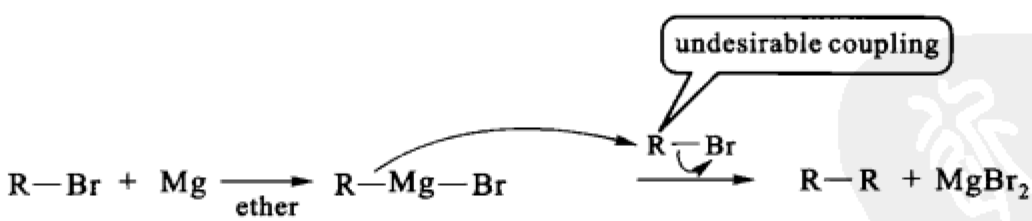


PROBLEM 14-17

Recall from Section 10-6 how acetylide ions are alkylated by displacing unhindered alkyl halides.



Like acetylide ions, Grignard and organolithium reagents are strong bases and strong nucleophiles. Luckily, however, they do not displace halides as easily as acetylide ions do. If they did displace alkyl halides, it would be impossible to form the reagents from alkyl halides because whenever a molecule of reagent formed, it would react with a molecule of starting material. All that would be formed is a coupling product. In fact, coupling is a side reaction that hurts the yield of many Grignard reactions.



If we *want* to couple two groups together, we can do it by using an organocopper reagent, a **lithium dialkylcuprate**, to couple with an alkyl halide.

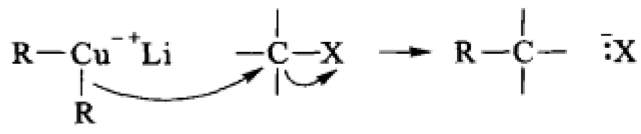
$$R_2CuLi + R'—X \longrightarrow R—R' + R—Cu + LiX$$

a lithium dialkylcuprate(二烷基铜锂)

The lithium dialkylcuprate (also called a *Gilman reagent*) is formed by the reaction of two equivalents of the corresponding organolithium reagent with cuprous iodide:

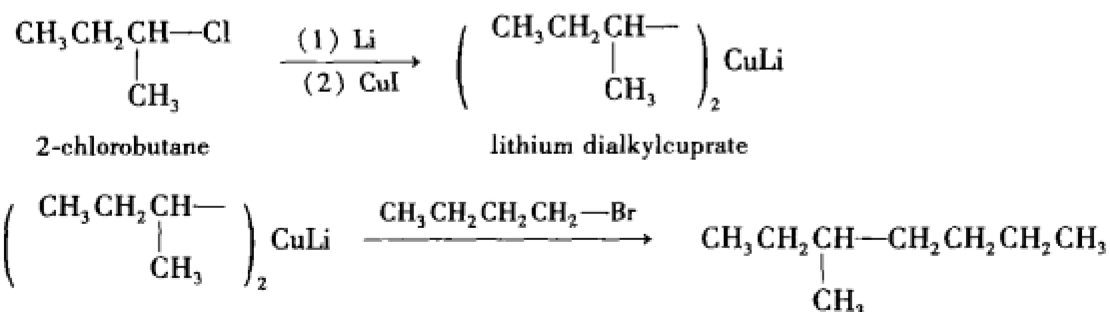
$$2R—Li + CuI \longrightarrow R_2CuLi + LiI$$

The coupling takes place as if a carbanion ($R\!:^-$) were present and the carbanion attacked the alkyl halide to displace the halide ion. This is not necessarily the actual mechanism, however.



(hypothetical mechanism)

Example



2-chlorobutane lithium dialkylcuprate

lithium dialkylcuprate 3-methylheptane(70%)

Show how you would synthesize the following compounds from alkyl halides, vinyl halides, and aryl halides containing no more than six carbon atoms.

(a) *n*-octane **(b)** vinylcyclohexane

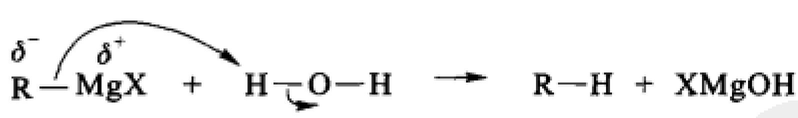
(c) *n*-butylcyclohexane **(d)** *trans*-3-octene

14-8 Side Reactions of Organometallic Reagents: Reduction of Alkyl Halides

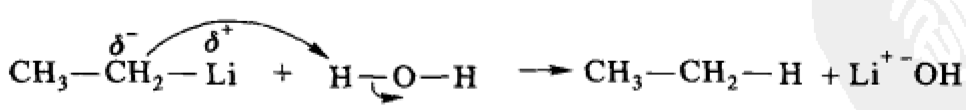
Grignard and organolithium reagents are strong nucleophiles and strong bases. Besides their additions to carbonyl compounds, they react with other acidic or electrophilic compounds. In some cases, these are useful reactions, but they are often seen as annoying side reactions where a small impurity of water or an alcohol destroys the reagent.

14-8A Reactions with Acidic Compounds

Grignard and organolithium reagents react vigorously and irreversibly with water. Therefore, all reagents and solvents used in these reactions must be dry.



For example, consider the reaction of ethyllithium with water:



ethyllithium(乙基锂) ethane

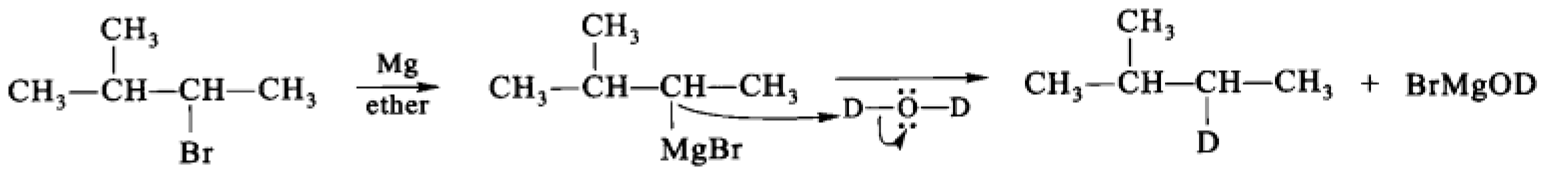
The products are strongly favored in this reaction. Ethane is a *very* weak acid(K_a of about 10^{-50}), so the reverse reaction (abstraction of a proton from ethane by lithium hydroxide) is unlikely. When ethyllithium is added to water, ethane instantly bubbles to the surface.

Why would we ever want to add an organometallic reagent to water? This is a method for reducing an alkyl halide to an alkane:

$$\text{R—X} + \text{Mg} \xrightarrow[\text{ether}]{} \text{R—MgX} \xrightarrow{H_2O} \text{R—H} + \text{XMgOH}$$

$$R{-}X \quad + \quad 2Li \longrightarrow R{-}Li \quad + \quad LiX \xrightarrow{H_2O} R{-}H \quad + LiOH$$

The overall reaction is a *reduction* because it replaces the electronegative halogen atom with a hydrogen atom. In particular, this reaction provides a way to "label" a compound with deuterium (^2H, a heavy isotope of hydrogen) at any position where a halogen is present.



In addition to O—H groups, the protons of N—H and S—H groups and the hydrogen atom of a terminal alkyne, —C≡C—H, are sufficiently acidic to protonate Grignard and organolithium reagents. Unless we want to protonate the reagent, compounds with these groups are considered incompatible with Grignard and organolithium reagents.

$$CH_3CH_2CH_2CH_2Li \ + \ (CH_3CH_2)_2NH \longrightarrow CH_3CH_2CH_2CH_3 \ + \ (CH_3CH_2)_2N^- \ Li^+$$

$$CH_3CH_2CH_2CH_2Li \ + \ CH_3(CH_2)_4{-}C{\equiv}C{-}H \longrightarrow CH_3CH_2CH_2CH_3 \ + \ CH_3(CH_2)_4{-}C{\equiv}C{-}Li$$

14-8B Reactions with Electrophilic Multiple Bonds

Grignard reagents are useful because they add to the electrophilic double bonds of carbonyl groups. However, we must make sure that the *only* electrophilic double bond in the solution is the one we want the reagent to attack. There must be no electrophilic double (or triple) bonds in the solvent or in the Grignard reagent itself, or they will be attacked as well. Any multiple bond involving a strongly electronegative element is likely to be attacked, including C=O, S=O, C=N, N=O, and C≡N bonds.

In later chapters, we will encounter methods for *protecting* susceptible groups to prevent the reagent from attacking them. For now, simply remember that the following groups react with Grignard and organolithium reagents; avoid compounds containing these groups except for the one carbonyl group that gives the desired reaction.

Protonate the Grignard or organolithium: O—H, N—H, S—H, —C≡C—H

Attacked by the Grignard or organolithium: C=O, C=N, C≡N, S=O, N=O

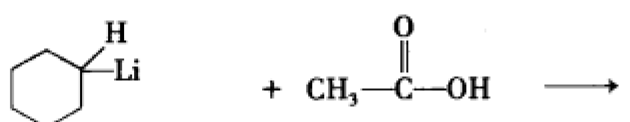
PROBLEM 14-18

Predict the products of the following reactions.

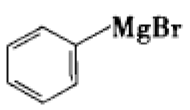
(a) methylmagnesium iodide + D_2O ⟶

(b) *n*-butyllithium + CH_3CH_2OH ⟶

(c) isobutylmagnesium bromide + 1-butyne ⟶

(d)  ⟶

cyclohexyllithium(环己基锂) acetic acid

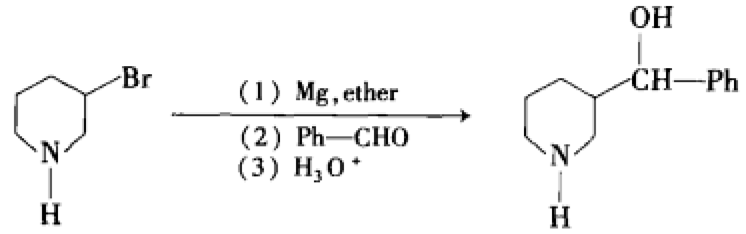
(e)  + D_2O ⟶

phenylmagnesium bromide

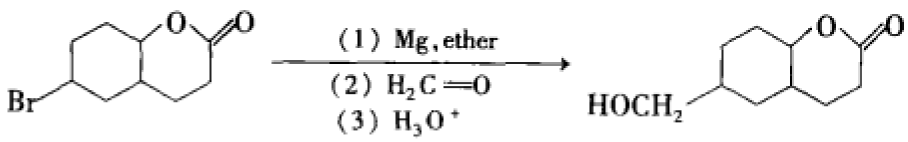
PROBLEM 14-19

Point out the flaws in the following incorrect Grignard syntheses.

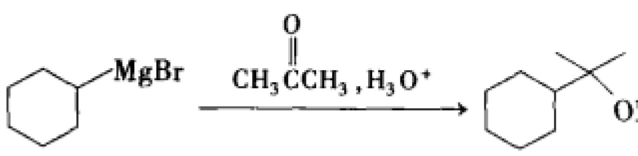
(a)



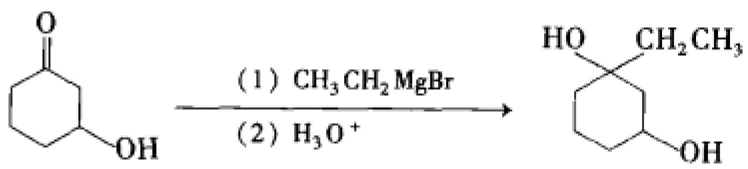
(b)



(c)



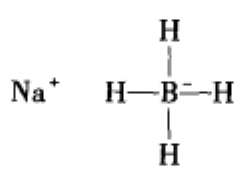
(d)



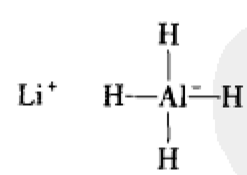
14-9 Synthesis of 1° and 2° Alcohols: Reduction of the Carbonyl Group

Grignard reagents convert carbonyl compounds to alcohols by adding alkyl groups. **Hydride reagents** add a hydride ion($H:^-$), reducing the carbonyl group to an alkoxide ion with no additional carbon atoms. Subsequent protonation gives the alcohol. Converting a ketone or an aldehyde to an alcohol involves adding two hydrogen atoms across the C=O bond: a reduction. Mechanism 14-2 shows the mechanism for this reduction.

The two most useful hydride reagents, sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$), reduce carbonyl groups in excellent yields. These reagents are called *complex hydrides* because they do not have a simple hydride structure such as Na^+H^- or Li^+H^-. Instead, their hydrogen atoms, bearing partial negative charges, are covalently bonded to boron and aluminum atoms. This arrangement makes the hydride a better nucleophile while reducing its basicity.



sodium borohydride(硼氢化钠)

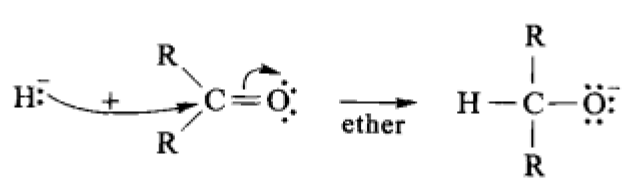


lithium aluminum hydride(氢化锂铝)

MECHANISM 14-2 Hydride Reduction of a Carbonyl Group

Sodium borohydride and lithium aluminum hydride reduce ketones and aldehydes to alcohols.

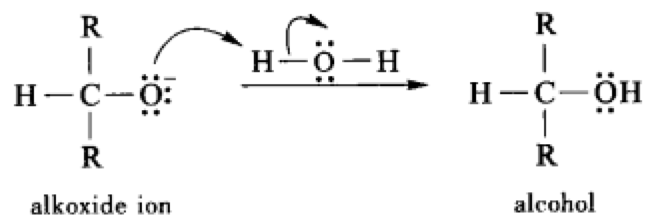
Reaction 1: Nucleophilic attack by hydride ion forms an alkoxide ion.



hydride ion(氢负离子)

alkoxide ion

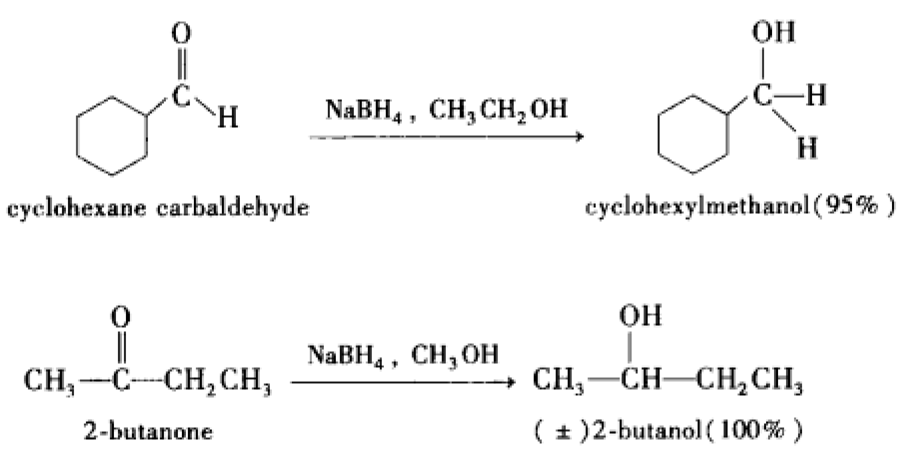
***Reaction 2*:** After the first reaction is complete, water or dilute acid is added to protonate the alkoxide.

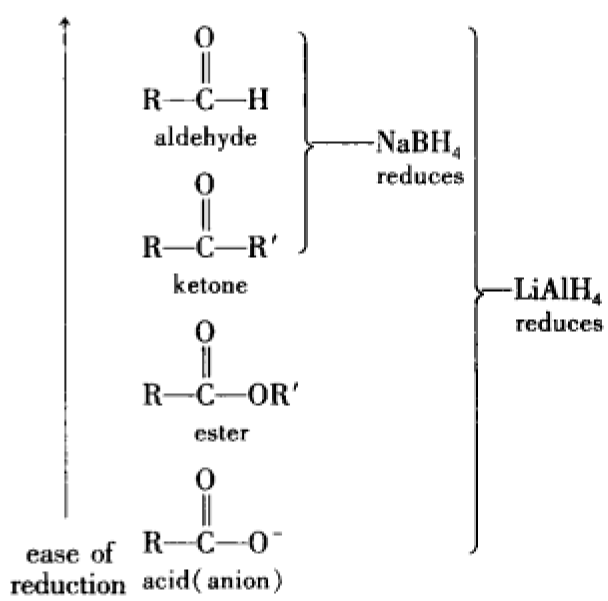


Aluminum is less electronegative than boron, so more of the negative charge in the AlH_4^- ion is borne by the hydrogen atoms. Therefore, lithium aluminum hydride is a much stronger reducing agent, and it is much more difficult to work with than sodium borohydride. LAH reacts explosively with water and alcohols, liberating hydrogen gas and sometimes starting fires. Sodium borohydride reacts slowly with alcohols and with water as long as the pH is high (basic). Sodium borohydride is a convenient and highly selective reducing agent.

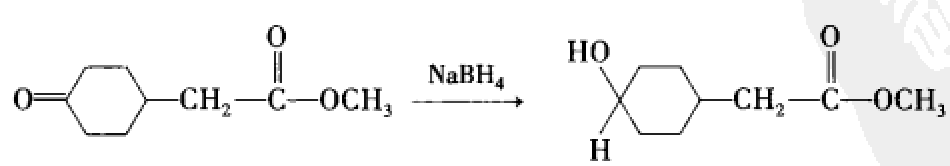
14-9A Uses of Sodium Borohydride

Sodium borohydride ($NaBH_4$) reduces aldehydes to primary alcohols, and ketones to secondary alcohols. The reactions take place in a wide variety of solvents, including alcohols, ethers, and water. The yields are generally excellent.



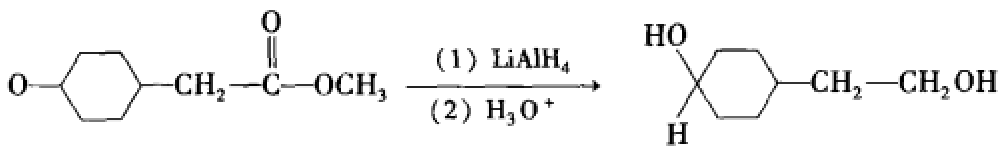


Sodium borohydride is selective; it usually does not react with carbonyl groups that are less reactive than ketones and aldehydes. For example, carboxylic acids and esters are unreactive toward borohydride reduction. Thus, sodium borohydride can reduce a ketone or an aldehyde in the presence of an acid or an ester.



14-9B Uses of Lithium Aluminum Hydride

Lithium aluminum hydride ($LiAlH_4$, abbreviated LAH) is a much stronger reagent than sodium borohydride. It easily reduces ketones and aldehydes and also the less-reactive carbonyl groups: those in acids, esters, and other acid derivatives. LAH reduces ketones to secondary alcohols, and it reduces aldehydes, acids, and esters to primary alcohols. The lithium salt of the alkoxide ion is initially formed, then the (cautious!) addition of dilute acid protonates the alkoxide. For example, LAH reduces both functional groups of the keto ester in the previous example.



In summary, sodium borohydride is the best reagent for reduction of a simple ketone or aldehyde. Using $NaBH_4$, we can reduce a ketone or an aldehyde in the presence of an acid or an ester, but we do not have a method (so far) for reducing an acid or an ester in the presence of a ketone or an aldehyde. The sluggish acid or ester requires the use of $LiAlH_4$, and this reagent also reduces the ketone or aldehyde.

SUMMARY Reactions of $LiAlH_4$ and $NaBH_4$

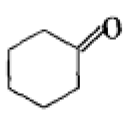
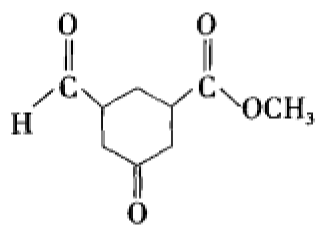
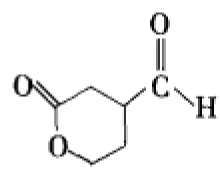
		$NaBH_4$	$LiAlH_4$
aldehyde	R—C(=O)—H	R—CH_2—OH	R—CH_2—OH
ketone	R—C(=O)—R′	R—CH(OH)—R′	R—CH(OH)—R′
alkene	>C=C<	no reaction	no reaction
acid anion	R—C(=O)—O^- (anion in base)	no reaction	R—CH_2—OH
ester	R—C(=O)—OR′	no reaction	R—CH_2—OH

Note: The products shown are the final products, after hydrolysis of the alkoxide.

PROBLEM 14-20

Predict the products you would expect from the reaction of $NaBH_4$ with the following compounds.

(a) $CH_3—(CH_2)_8—CHO$ (b) $CH_3CH_2—C(=O)—OCH_3$ (c) Ph—COOH

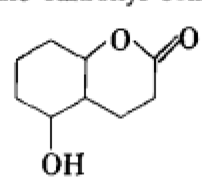
(d)  (e)  (f) 

PROBLEM 14-21

Repeat Problem 14-20 using $LiAlH_4$ (followed by hydrolysis) as the reagent.

PROBLEM 14-22

Show how you would synthesize the following alcohols by reducing appropriate carbonyl compounds.

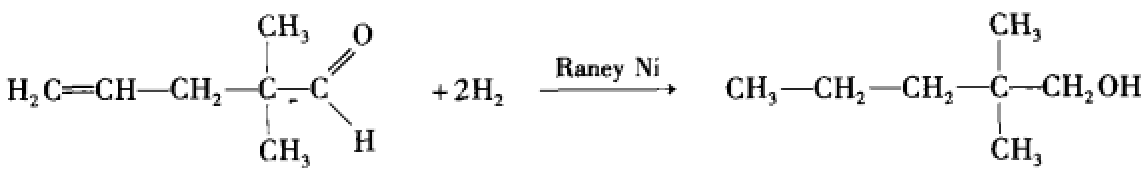
(a) 1-heptanol (b) 2-heptanol (c) 2-methyl-3-hexanol (d) 

14-9C Catalytic Hydrogenation of Ketones and Aldehydes

Reducing a ketone or an aldehyde to an alcohol involves adding two hydrogen atoms across the C=O bond. This

addition can be accomplished by catalytic hydrogenation, commonly using Raney nickel as the catalyst.

Raney nickel is a finely divided hydrogen-bearing form of nickel made by treating a nickel-aluminum alloy with a strong sodium hydroxide solution. The aluminum in the alloy reacts to form hydrogen, leaving behind a finely divided nickel powder saturated with hydrogen. Raney nickel is an effective catalyst for the hydrogenation of ketones and aldehydes to alcohols. Carbon-carbon double bonds are also reduced under these conditions, however, so any alkene double bonds in the starting material will also be reduced. In most cases, sodium borohydride is more convenient for reducing simple ketones and aldehydes.



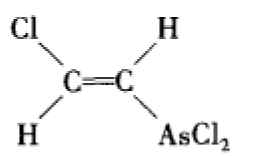
2,2-dimethyl-4-pentenal → 2,2-dimethyl-1-pentanol(94%)

NaBH₄ (for comparison) → 2,2-dimethylpent-4-en-1-ol

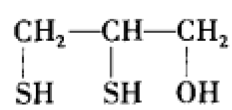
14−10 Thiols (Mercaptans)

The odor of thiols is their strongest characteristic. **Skunk** scent is composed mainly of 3-methyl-1-butanethiol and 2−butene−1−thiol, with small amounts of other thiols. Ethanethiol is added to natural gas(odorless methane) to give it the characteristic "gassy" odor for detecting leaks.

Thiols'ability to complex heavy metals has proved useful for making antidotes to heavy-metal poisoning. For example, in World War Ⅱ the Allies were concerned that the Germans would use lewisite, a volatile arsenic compound, as a chemical warfare agent. Thiols complex strongly with arsenic, and British scientists developed dimercaprol (2,3-dimercapto-1-propanol) as an effective antidote. The Allies came to refer to this compound as "British anti-lewisite"(BAL), a name that is still used. Dimercaprol is useful against a variety of heavy metals, including arsenic, mercury, and gold.



lewisite(路易斯毒气)



dimercaprol(二巯基丙醇)
British anti-lewisite(BAL)

Although oxygen is more electronegative than sulfur, thiols are more acidic than alcohols. Their enhanced acidity results from two effects: First, S—H bonds are generally weaker than O—H bonds, making S—H bonds easier to break. Second, the **thiolate ion** ($R{-}S^-$) has its negative charge on sulfur, which allows the charge to be delocalized over a larger region than the negative charge of an alkoxide ion, borne on a smaller oxygen atom. Thiolate ions are easily formed by treating the thiol with aqueous sodium hydroxide.

$$\underset{\substack{\text{ethanethiol(乙硫醇)} \\ pK_a = 10.5}}{CH_3{-}CH_2{-}SH} + {}^-OH \rightleftharpoons \underset{\text{ethanethiolate}}{CH_3{-}CH_2{-}S^-} + \underset{pK_a = 15.7}{H_2O}$$

benzenethiol(thiophenol, 苯硫酚) $pK_a = 7.8$ benzenethiolate $pK_a = 15.7$

For comparison

$$CH_3—CH_2—OH + {}^-OH \rightleftharpoons CH_3—CH_2—O^- + H_2O$$

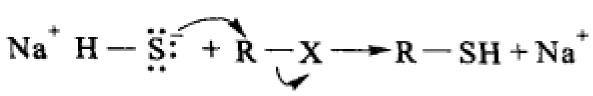
ethanol $pK_a = 15.9$ ethoxide $pK_a = 15.7$

PROBLEM 14-23

Arrange the following compounds in order of decreasing acidity.

CH_3COOH CH_3OH CH_3CH_3 CH_3SO_3H CH_3NH_2 CH_3SH $CH_3C{\equiv}CH$

Thiols can be prepared by S_N2 reactions of sodium hydrosulfide with unhindered alkyl halides. The thiol product is still nucleophilic, so a large excess of hydrosulfide is used to prevent the product from undergoing a second alkylation to give a sulfide(R—S—R).



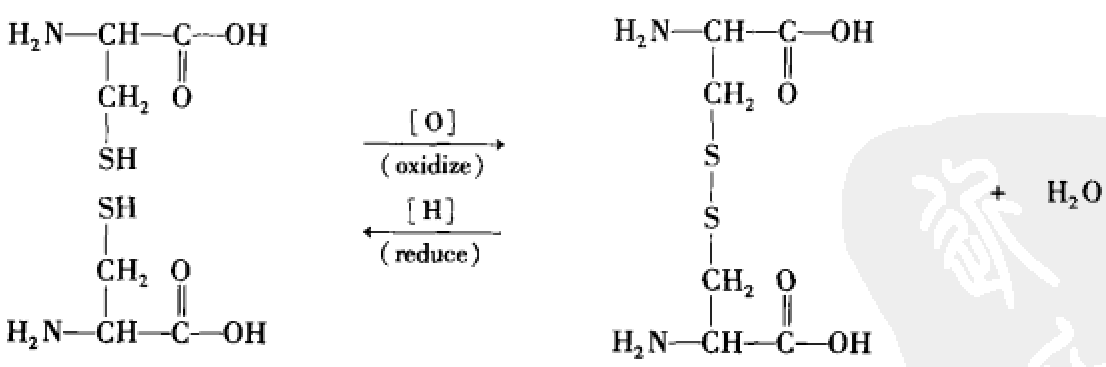
sodium hydrosulfide (硫氢化钠) alkyl halide thiol

Unlike alcohols, thiols are easily oxidized to give a dimer called a **disulfide**. The reverse reaction, reduction of the disulfide to the thiol, takes place under reducing conditions. Formation and cleavage of disulfide linkages is an important aspect of protein chemistry, where disulfide "bridges" between cysteine amino acid residues hold the protein chain in its active conformation.

$$R—SH + HS—R \underset{Zn,\ HCl}{\overset{Br_2}{\rightleftharpoons}} R—S—S—R + 2\ HBr$$

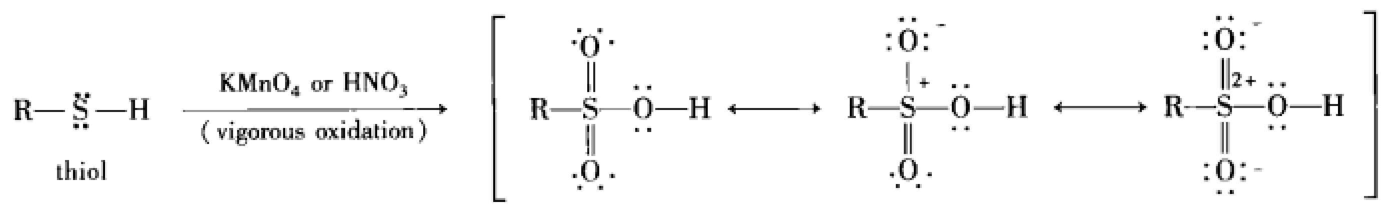
two molecules of thiol disulfide(二硫化物)

Example



two cysteine residues(半胱氨酸残基) cystine disulfide bridge(胱氨酸二硫桥)

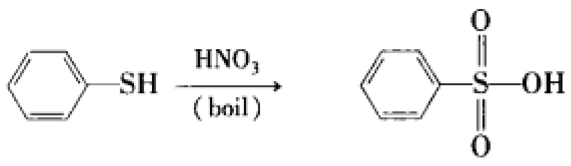
Just as mild oxidation converts thiols to disulfides, vigorous oxidation converts them to **sulfonic acids**. $KMnO_4$ or nitric acid (HNO_3), or even bleach (NaOCl) can be used as the oxidant for this reaction. Any Lewis structure of a sulfonic acid requires either separation of formal charges or more than 8 electrons around sulfur. Sulfur can have an expanded octet, as it does in SF_4 (10 electrons) and SF_6 (12 electrons). The three resonance forms shown here are most commonly used. Organic chemists tend to use the form with an expanded octet, and inorganic chemists tend to use the forms with charge separation.



thiol; expanded octet; (both); charge separation

sulfonic acid(磺酸)

Example



benzenethiol　　benzenesulfonic acid(苯磺酸)

PROBLEM 14-24

Authentic skunk spray has become valuable for use in scent-masking products. Show how you would synthesize the two major components of skunk spray (3-methylbutane-1-thiol and 2-butene-1-thiol) from any of the readily available butenes or from 1,3-butadiene.

Summary in Chinese

本 章 概 要

一、醇的结构

在醇分子的 C—O 键中,碳和氧原子均为 sp^3 杂化,C—O—H 的键角约 109°。醇羟基是一个极性较强的基团,因此低碳数醇分子极性较强,醇羟基决定了醇类化合物的主要物理性质和化学性质。小分子醇是常用的极性质子型溶剂。醇羟基(—OH)与伯碳相连称为伯醇(RCH_2OH),与仲碳相连称为仲醇(RR′CHOH),与叔碳相连称为叔醇(RR′R″COH),醇羟基(—OH)与苯环相连称为酚。

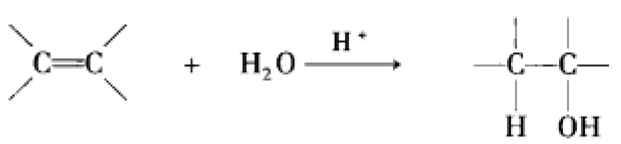
二、醇的物理性质

醇分子间氢键使醇的沸点明显高于与其相对分子质量相似的烃、醚、卤代烃及醛、酮等化合物。醇能与水形成氢键,小分子醇具有良好的水溶性。醇的碳链增长,其在水中的溶解度明显减小。

三、醇的制备

1. 由烯烃制备醇 (from alkenes to alcohols):

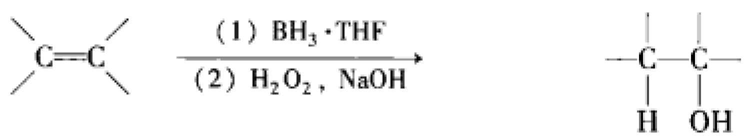
(1) 酸催化加水反应 (acid-catalyzed hydration, Section 9-4):



Markovnikov orientation

☆ 反应经过碳正离子中间体,伯、仲碳正离子可能发生重排,反应符合马氏规则。

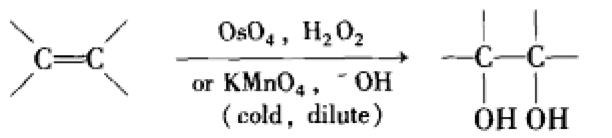
(2) 硼氢化-氧化反应 (hydroboration-oxidation, Section 9-7):



syn addition, anti-Markovnikov orientation

☆ 反应经过协同加成机理，OH、H 顺式加成到烯烃双键上，反马式定向。

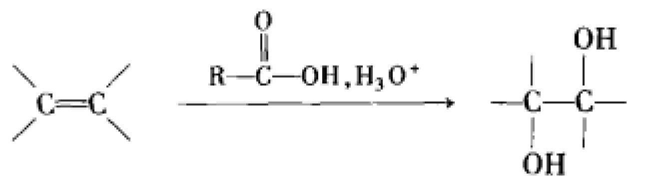
（3）烯烃顺式二羟基化反应（syn hydroxylation，Section 9－14）：



syn hydroxylation

☆ 反应经过五元环锇酸酯或五元环锰酸酯中间体，由此生成顺式加成产物。镜面对称的顺式烯烃生成内消旋邻二醇，而中心对称的反式烯烃和不对称烯烃生成外消旋邻二醇。用高浓度 $KMnO_4$、酸性介质或加热时，烯烃双键彻底断裂生成酮和羧酸，端烯烃碳生成 CO_2。

（4）反式二羟基化反应（anti hydroxylation，Section 9－13）：



anti hydroxylation

☆ 反应经过三元环氧化物中间体，酸催化水解开环，生成反式加成产物。中心对称的反式烯烃生成内消旋邻二醇，而镜面对称的顺式烯烃和不对称烯烃生成外消旋邻二醇。

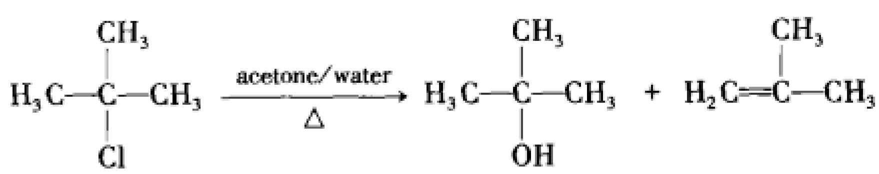
2. 由卤代烷制备醇（from alkyl halides to alcohols）：

（1）伯卤代烷及空阻小的仲卤代烷亲核取代反应（nucleophilic substitution of primary alkyl halides and some unhindered secondary alkyl halides，Section 7－8）：

$$(CH_3)_2CHCH_2CH_2—Br \xrightarrow[H_2O]{KOH} (CH_3)_2CHCH_2CH_2—OH$$

☆ 反应经过 S_N2 机理进行，^-OH 从离去基团反面进攻，被进攻碳构型转化，立体选择性反应，不发生重排，一般用于合成伯醇或空阻小的仲醇。

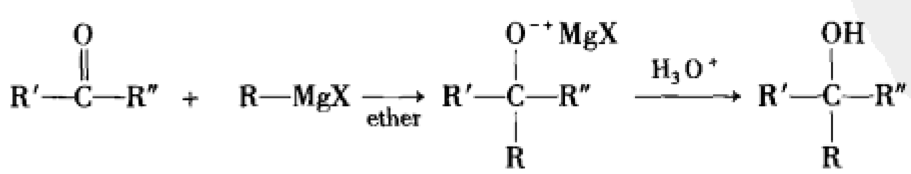
（2）叔卤代烷及仲卤代烷亲核取代反应（nucleophilic substitution of tertiary and secondary alkyl halides，Section 7－12）：

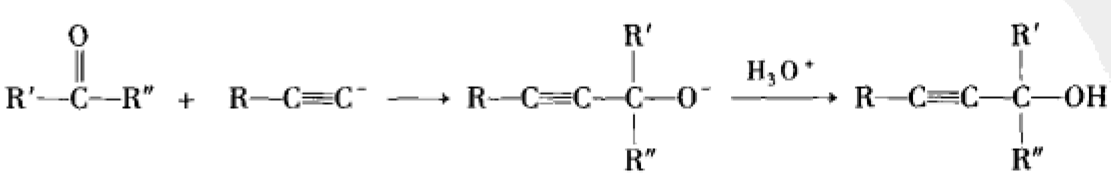


☆ 反应经过 S_N1 机理进行，经过碳正离子中间体，可能发生重排，无立体选择性；副产物为烯烃，可用于合成叔醇或仲醇。

3. 由羰基化合物或环氧乙烷制备醇（from carbonyl compounds or ethylene oxide to alcohols）：

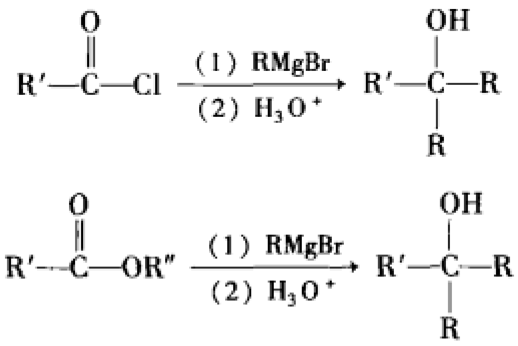
（1）醛、酮羰基亲核加成反应（nucleophilic addition to the carbonyl group of aldehydes and ketones，Section 14－7A）：





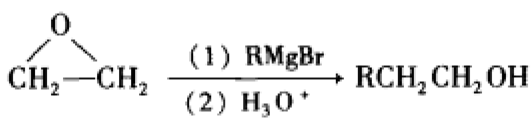
☆ 甲醛加成生成伯醇，其他醛加成生成仲醇，酮加成生成叔醇。格氏试剂和有机锂试剂与活泼氢，如 OH、NH、SH、C≡CH 等，快速反应生成 RH；除羰基外，其他极性不饱和键，如 C═S、C═N、S═O、N═O、C≡N 等都能与格氏试剂和有机锂试剂反应。因此，反应物醛、酮分子中不能有活泼氢和以上不饱和官能团，反应必须在无水的极性质子型溶剂中进行，如乙醚、四氢呋喃等。

(2) 酰氯、酯羰基亲核加成反应 (nucleophilic addition to the carbonyl group of acid halides and esters, Section 14-7B)：



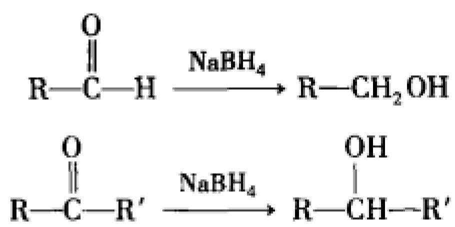
☆ 两种反应的第一步均为羰基亲核取代反应，经过酮中间体，当反应试剂为 RMgCl 或 RLi 时，反应难以停留在酮阶段，第二分子 RMgCl 或 RLi 容易与中间体酮的羰基进一步发生亲核加成反应，生成叔醇。R_2CuLi 的活性低于 RMgCl 和 RLi，酰氯与 R_2CuLi 反应可以停留在酮阶段。反应注意事项与醛、酮羰基亲核加成反应相同。

(3) 环氧乙烷亲核开环反应 (nucleophilic ring-opening reaction of ethylene oxide, Section 14-7C)：



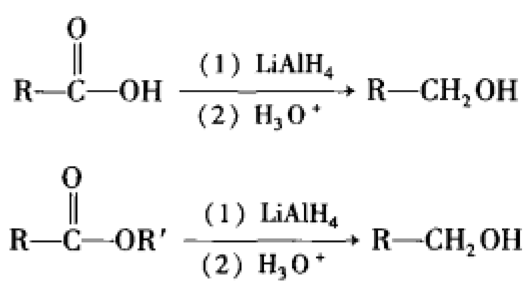
☆ RMgX 与环氧乙烷的亲核开环反应可用于合成 R 碳链增长 2 个碳的伯醇。反应注意事项与醛、酮羰基亲核加成反应相同。

(4) 醛、酮还原反应 (reduction of aldehydes and ketones, 14-9A)



☆ 醛还原生成伯醇，酮还原生成仲醇。$NaBH_4$ 不还原碳碳双键、羧酸、酯和酰胺，可还原亚胺 (—C═N—) 至伯胺 ($—CH_2NH_2$)，还原酰卤 (—COX) 至伯醇 ($—CH_2OH$)。

(5) 羧酸或酯还原生成伯醇 (reduction of an acid or ester to a primary alcohol, 14-9B)：



☆ $LiAlH_4$ 对水和质子型溶剂非常活泼，反应必须在严格无水条件下进行。$LiAlH_4$ 不还原碳碳双键，可还原—C═N—、—C≡N、$—NO_2$ 至伯胺，还原—COX、$—CONH_2$ 至伯醇。

(6) 醛、酮催化加氢 (catalytic hydrogenation of aldehydes and ketones, Section 14-9C)

☆ 催化加氢为强还原条件，可还原分子中的碳碳双键和三键，亦可还原—C ═N—、—C≡N 、—NO_2 基团生成伯胺。以醛、酮为起始物催化加氢制备伯、仲醇时，分子中不能有其他易还原的不饱和键。

四、硫醇（Thiols）

1. 硫醇的结构与性质：硫醇在结构上与醇相似。硫酚分子中的巯基（—SH）生成氢键的能力较弱，因此，硫醇、硫酚的沸点较相应的醇、酚低，并且在水中的溶解度明显小于相应的醇。硫醇的酸性比醇和水强，能与 NaOH 水溶液反应生成硫醇钠。

2. 硫醇的制备：一般醇的制备方法亦可用于制备硫醇，如 NaSH 或 KSH 与空阻小的卤代烷亲核取代反应可用于制备硫醇。

3. 硫醇的重要反应：

（1）硫醇与重金属离子的反应（reaction of thiols with heavy-metal ions）：

$$2\,RSH + M^{2+} \longrightarrow (RS)_2M\downarrow$$
$$M^{2+} = Hg^{2+}, Pb^{2+}$$

☆ 硫醇能与汞、铅等重金属离子反应，生成不溶于水的硫醇盐，可用于硫醇的分析鉴定或作为重金属中毒的解毒药。

（2）硫醇与弱氧化剂的反应（oxidation of thiols by weak oxidants）：

$$2\,RSH \underset{Zn,\ HCl}{\overset{\text{空气}}{\rightleftharpoons}} R{-}S{-}S{-}R + H_2O$$

☆ 硫醇比醇易氧化，在弱氧化剂（O_2、H_2O_2、I_2、Br_2）作用下，硫醇氧化生成过硫醚 RSSR。

（3）硫醇与强氧化剂的反应（oxidation of thiols by strong oxidants）：

$$R{-}SH \xrightarrow{KMnO_4\ \text{or}\ HNO_3} R{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}OH$$

Essential Problem-Solving Skills in Chapter 14

1. Predict relative boiling points, acidities, and solubilities of alcohols.
2. Show how to convert alkenes, alkyl halides, and carbonyl compounds to alcohols.
3. Predict the alcohol products of hydration, hydroboration, and hydroxylation of alkenes.
4. Use Grignard and organolithium reagents effectively for the synthesis of primary, secondary, and tertiary alcohols with the required carbon skeletons.
5. Propose syntheses and oxidation products of simple thiols.

Study Problems

14−25 Briefly define each term, and give an example.

(a) primary alcoho（伯醇） (b) secondary alcohol（仲醇） (c) tertiary alcohol（叔醇）
(d) phenol（苯酚） (e) diol（二醇） (f) glycol（乙二醇）
(g) alkoxide ion（烷氧基离子） (h) epoxide（环氧化物） (i) Grignard reagent（革氏试剂）
(j) organolithium reagent（有机锂试剂） (k) ketone（酮） (l) aldehyde（醛）
(m) carboxylic acid（羧酸） (n) acid chloride（酰氯） (o) ester（酯）
(p) hydride reagents（负氢试剂） (q) thiol（硫醇） (r) disulfide（二硫化物）

14−26 Predict which member of each pair has the higher boiling point, and explain the reasons for you predictions.

(a) 1-hexanol or 3,3-dimethyl-1-butanol (b) 2-hexanone or 2-hexanol

(**c**) 2-hexanol or 1,5-hexanediol (**d**) 2-pentanol or 2-hexanol

14−27 Predict which member of each pair is more acidic, and explain the reasons for your predictions.

(**a**) cyclopentanol or 3-chlorophenol (**b**) cyclohexanol or 2-chlorocyclohexanol

(**c**) cyclohexanol or cyclohexanecarboxylic acid (**d**) 2,2-dichloro-1-butanol or 1-butanol

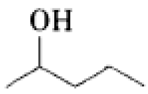
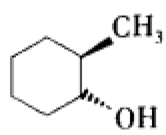
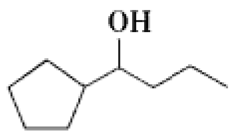
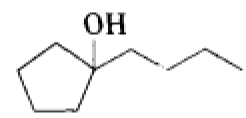
14−28 Predict which member of each group is most soluble in water, and explain the reasons for your predictions.

(**a**) 1-butanol, 1-pentanol, or 2-propanol

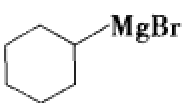
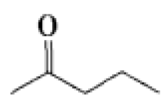
(**b**) chlorocyclohexane, cyclohexanol, or 1,2-cyclohexanediol

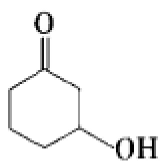
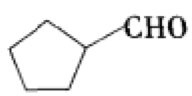
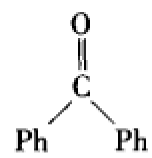
(**c**) chlorocyclohexane, cyclohexanol, or 4-methylcyclohexanol

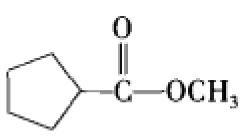
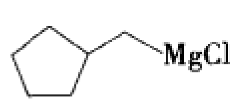
14−29 Show how you would synthesize the following alcohols from appropriate alkenes.

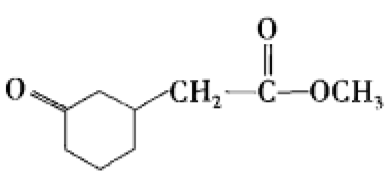
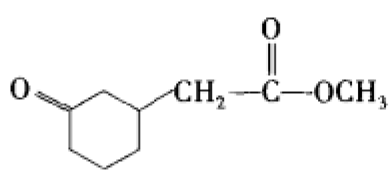
(**a**)  (**b**)  (**c**)  (**d**) 

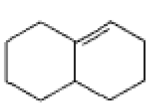
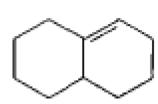
14−30 Draw the organic products you would expect to isolate from the following reactions (after hydrolysis).

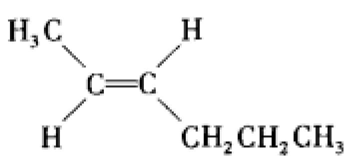
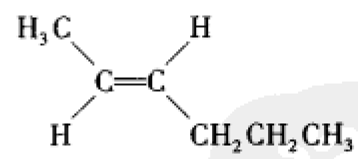
(**a**)  + $H_2C{=}O$ (**b**) +  (**c**) CH_3—CH(MgI)—CH_3 + Ph—CHO

(**d**) CH_3MgI +  (**e**)  + $NaBH_4$ (**f**) Ph—MgBr + 

(**g**) 2 Ph—MgBr +  (**h**) 2  + Ph—C(=O)—Cl

(**i**)  + $NaBH_4$ (**j**)  + $LiAlH_4$

(**k**)  (1) $Hg(OAc)_2, H_2O$; (2) $NaBH_4$ (**l**)  (1) $BH_3 \cdot THF$; (2) H_2O_2, ^-OH

(**m**)  cold, dilute $KMnO_4$, ^-OH (**n**)  HCO_3H, H_3O^+

(**o**) $(CH_2{=}CH)_2CuLi$ + $CH_3CH_2CH{=}CHCH_2Br$

14−31 Show how you would use Grignard syntheses to prepare the following alcohols from the indicated starting materials and any other necessary reagents.

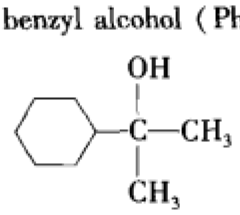
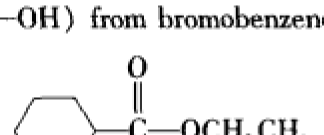
(**a**) 3-octanol from hexanal, $CH_3(CH_2)_4CHO$

(**b**) 1-octanol from 1-bromoheptane

(**c**) 1-cyclohexylethanol from acetaldehyde, CH_3CHO

(**d**) 2-cyclohexylethanol from bromocyclohexane

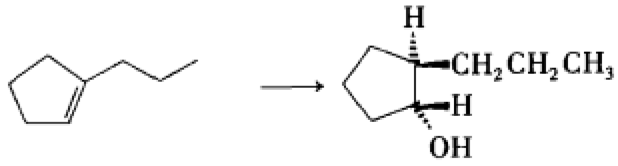
(**e**) benzyl alcohol (Ph—CH_2—OH) from bromobenzene (Ph—Br)

(**f**)  from 

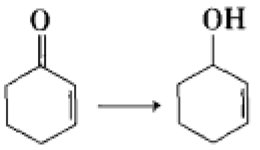
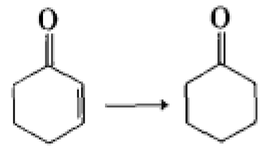
(**g**) cyclopentylphenylmethanol from benzaldehyde (Ph—CHO)

(**h**) 4-methylhept-2-yn-4-ol from 2-pentanone

14–32 Show how you would accomplish the following transformations. You may use any additional reagents you need.

(a) 

(b) Ph—CH_2CH_2Cl ⟶ Ph—$CH_2CH_2CH_2OH$

(c)  (d) 

(e) $CH_3—\overset{O}{\overset{\|}{C}}—CH_2CH_2—\overset{O}{\overset{\|}{C}}—OCH_2CH_3 \longrightarrow CH_3—\overset{OH}{\overset{|}{C}H}—CH_2CH_2—\overset{O}{\overset{\|}{C}}—OCH_2CH_3$

(f) $CH_3—\overset{O}{\overset{\|}{C}}—CH_2CH_2—\overset{O}{\overset{\|}{C}}—OCH_2CH_3 \longrightarrow CH_3—\overset{OH}{\overset{|}{C}H}—CH_2CH_2—\overset{OH}{\overset{|}{C}H_2}$

14–33 Show how you would synthesize

(a) 2-phenylethanol by the addition of formaldehyde to a suitable Grignard reagent

(b) 2-phenylethanol from a suitable alkene

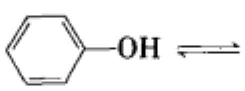
(c) cyclohexylmethanol from an alkyl halide using an S_N2 reaction

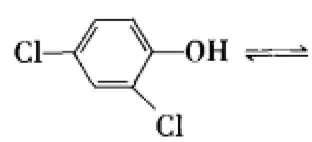
(d) 3-cyclohexyl-1-propanol by the addition of ethylene oxide to a suitable Grignard reagent

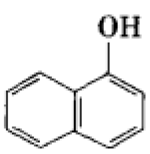
(e) *cis*-pent-2-en-1-thiol from a suitable alkenyl halide

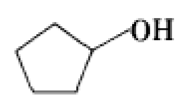
(f) 2,5-dimethylhexane from a four-carbon alkyl halide

14–34 Complete the following acid-base reactions. In each case, indicate whether the equilibrium favors the reactants or the products, and explain your reasoning.

(a) $CH_3CH_2—O^-$ +  ⇌

(b) KOH +  ⇌

(c)  + CH_3O^- ⇌

(d)  + KOH ⇌

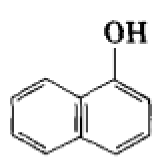
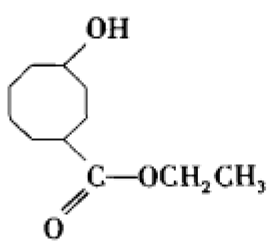
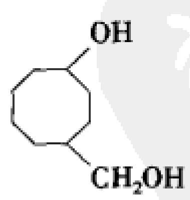
(e) $(CH_3)_3C—O^-$ + CH_3CH_2OH ⇌

(f) $(CH_3)_3C—O^-$ + H_2O ⇌

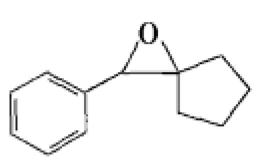
(g) KOH + CH_3CH_2OH ⇌

14–35 Suggest carbonyl compounds and reducing agents that might be used to form the following alcohols.

(a) *n*-octanol (b) 1-cyclohexyl-1-propanol (c) 1-phenyl-1-butanol

(d)  (e)  (f) 

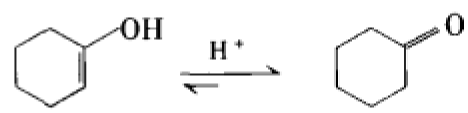
14–36 Show how you would synthesize the following compound from any starting materials containing no more than six carbon atoms.



14–37 Vinyl alcohols are generally unstable, quickly isomerizing to carbonyl compounds. Propose mechanisms for the following isomerizations.

(a)

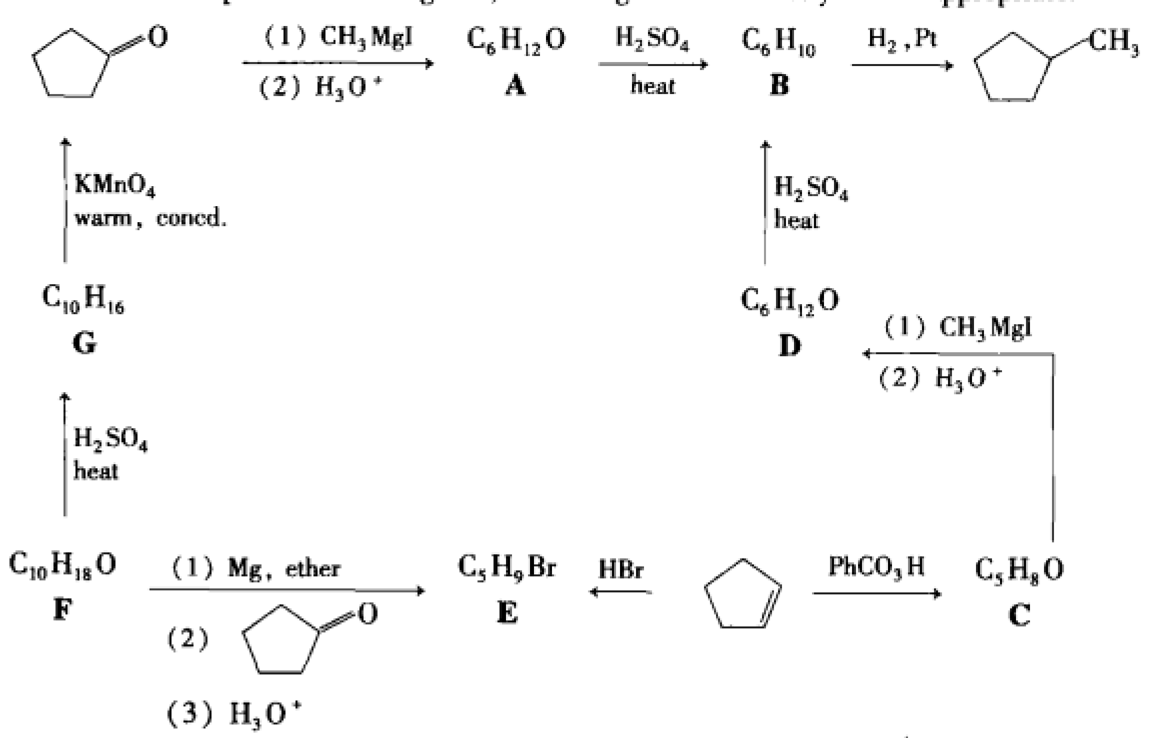
vinyl alcohol (乙烯醇)　　acetaldehyde (乙醛)

(b) 

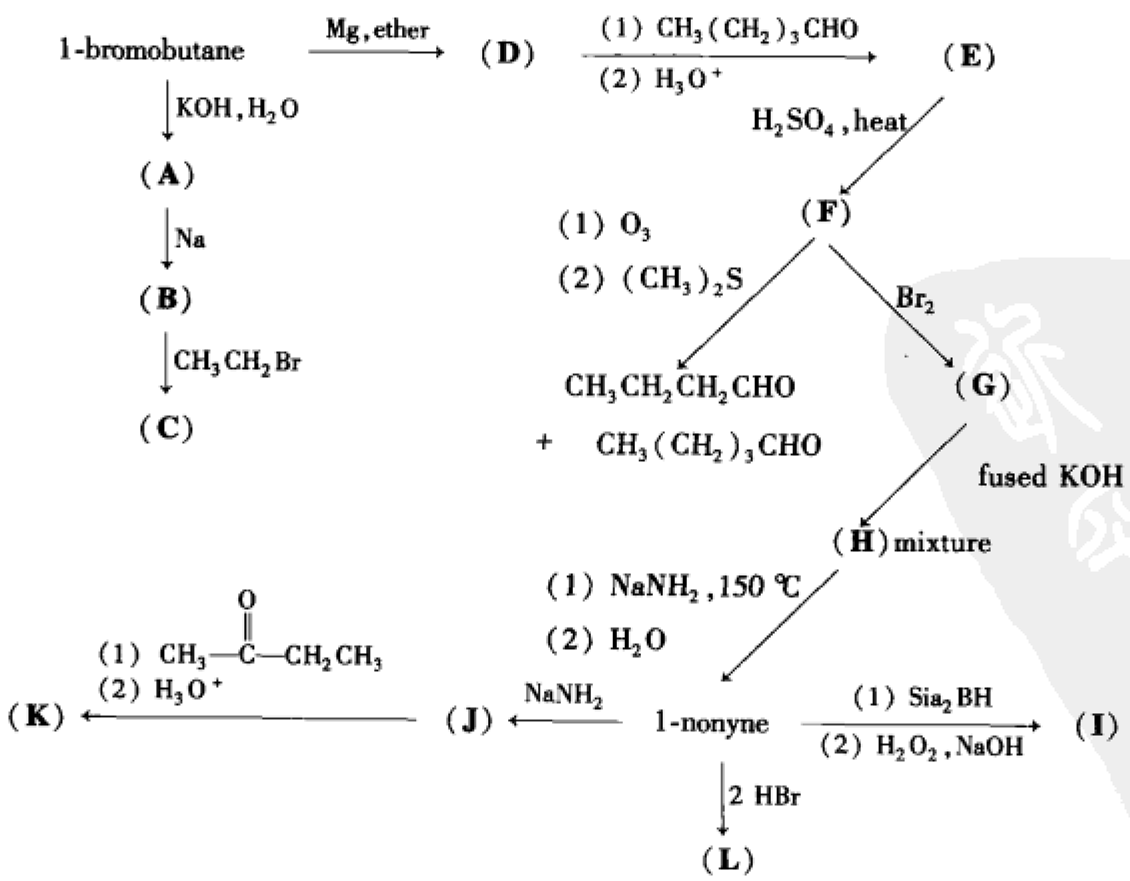
(c)

***14–38** Compound **A** ($C_7H_{11}Br$) is treated with magnesium in ether to give **B** ($C_7H_{11}MgBr$), which reacts violently with D_2O to give 1-methylcyclohexene with a deuterium atom on the methyl group (**C**). Reaction of **B** with acetone (CH_3COCH_3) followed by hydrolysis gives **D** ($C_{10}H_{18}O$). Heating **D** with concentrated H_2SO_4 gives **E**($C_{10}H_{16}$), which decolorizes two equivalents of Br_2 to give **F** ($C_{10}H_{16}Br_4$). **E** undergoes hydrogenation with excess H_2 and a Pt catalyst to give isobutylcyclohexane. Determine the structures of compounds **A** through **F**, and show your reasoning throughout.

***14–39** Determine the structures of compounds **A** through **G**, including stereochemistry where appropriate.



14–40 Propose structures for intermediates and products (**A**) through (**L**).



Chapter 15
Reactions of Alcohols

Alcohols are important organic compounds because the hydroxyl group is easily converted to almost any other functional group. In Chapter 14, we studied reactions that form alcohols. In this chapter, we seek to understand how alcohols react and which reagents are best for converting them to other kinds of compounds.

15-1 Oxidation States of Alcohols and Related Functional Groups

Oxidation of alcohols leads to ketones, aldehydes, and carboxylic acids. These functional groups, in turn, undergo a wide variety of additional reactions. For these reasons, alcohol oxidations are some of the most common organic reactions.

In inorganic chemistry, we think of oxidation as a loss of electrons and reduction as a gain of electrons. Most organic compounds are uncharged, however, and gain or loss of electrons is not obvious. Organic chemists tend to think of **oxidation** as the result of adding an oxidizing agent (O_2, Br_2, etc.), and **reduction** as the result of adding a reducing agent (H_2, $NaBH_4$, etc.). Most organic chemists habitually use the following simple rules, based on the change in the formula of the substance:

OXIDATION: addition of O or O_2; addition of X_2 (halogens); loss of H_2.

REDUCTION: addition of H_2 (or H^-); loss of O or O_2; loss of X_2.

NEITHER: addition or loss of H^+, H_2O, HX, etc. is neither an oxidation nor a reduction.

We can tell that an oxidation or a reduction of an alcohol has taken place by counting the number of C—O bonds to the carbon atom. For example, in a primary alcohol, the carbinol (C—OH) carbon atom has one bond to oxygen; in an aldehyde, the carbonyl carbon has two (more oxidized); and in an acid, it has three. Oxidation of an alcohol usually converts C—H bonds to C—O bonds. If we convert an alcohol to an alkane, the carbinol carbon loses its bond to oxygen and gains another bond to hydrogen.

Figure 15-1 compares the oxidation states of primary, secondary, and tertiary alcohols with those obtained by oxidation or reduction. The symbol [O] indicates an unspecified oxidizing agent. Notice that oxidation of a primary or secondary alcohol forms a carbonyl (C═O) group by the removal of two hydrogen atoms: one from the carbinol carbon and one from the hydroxyl group. A tertiary alcohol cannot easily oxidize because there is no hydrogen atom available on the carbinol carbon.

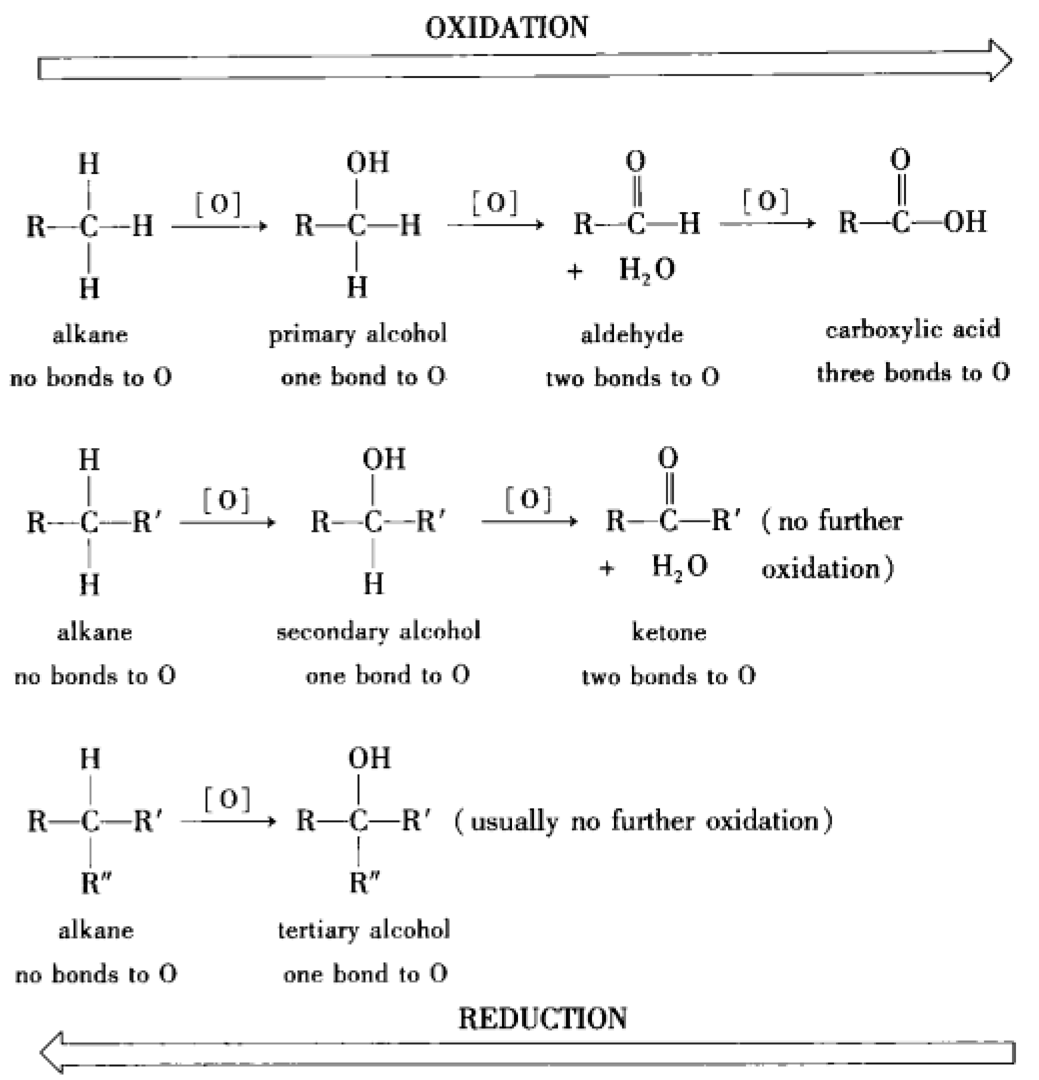


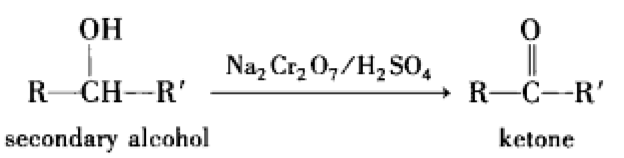
Figure 15-1 Oxidation states of alcohols. An alcohol is more oxidized than an alkane, yet less oxidized than carbonyl compounds such as ketones, aldehydes, and acids. Oxidation of a primary alcohol leads to an aldehyde, and further oxidation leads to an acid. Secondary alcohols are oxidized to ketones. Tertiary alcohols cannot be oxidized without breaking carbon-carbon bonds.

15-2 Oxidation of Alcohols

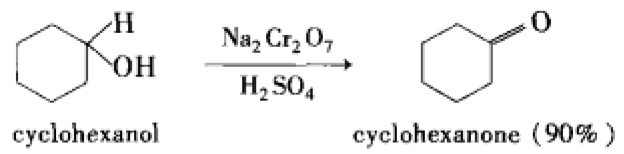
Primary and secondary alcohols are easily oxidized by a variety of reagents, including chromium reagents, permanganate, nitric acid, and even household bleach (NaOCl, sodium hypochlorite). The choice of reagent depends on the amount and value of the alcohol. We use cheap oxidants for large-scale oxidations of simple, inexpensive alcohols. We use the most effective and selective reagents, regardless of cost, for delicate and valuable alcohols. In this chapter, we study only the oxidants that have the widest range of uses and the best selectivity. An understanding of the most common oxidants can later be extended to include additional reagents.

15-2A Oxidation of Secondary Alcohols

Secondary alcohols are easily oxidized to give excellent yields of ketones. The **chromic acid reagent** is often best for laboratory oxidations of secondary alcohols.



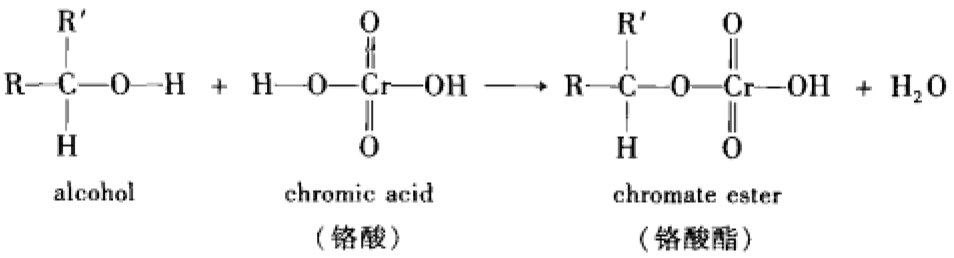
Example



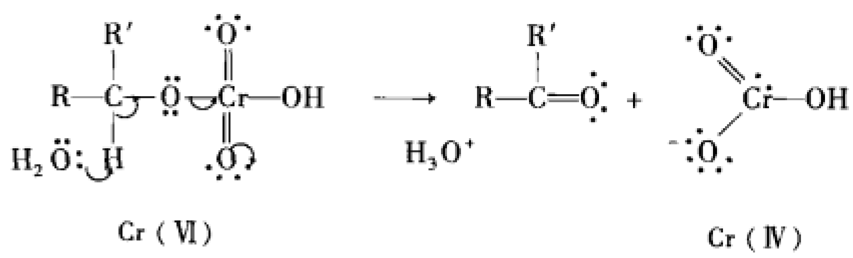
The chromic acid reagent is prepared by dissolving sodium dichromate ($Na_2Cr_2O_7$) in a mixture of sulfuric acid and water. The active species in the mixture is probably chromic acid, H_2CrO_4, or the acid chromate ion, $HCrO_4^-$. Adding chromium trioxide (CrO_3) to dilute sulfuric acid achieves the same result.

The mechanism of chromic acid oxidation probably involves the formation of a chromate ester. Elimination of the chromate ester gives the ketone. In the elimination, the carbinol carbon retains its oxygen atom but loses its hydrogen and gains the second bond to oxygen.

Formation of the chromate ester



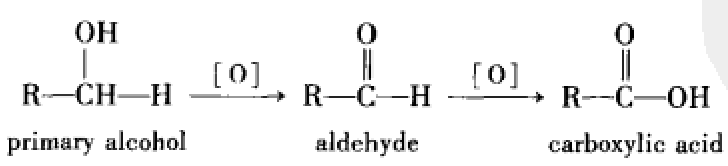
Elimination of the chromate ester and oxidation of the carbinol carbon



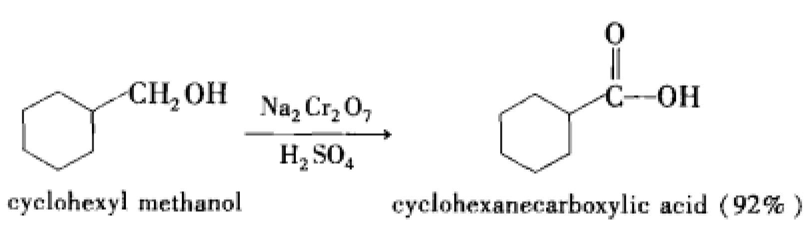
The chromium (Ⅳ) species formed reacts further to give the stable reduced form, chromium (Ⅲ). Both sodium dichromate and chromic acid are orange, while chromic ion (Ⅲ) is a deep blue. One can follow the progress of a chromic acid oxidation by observing the color change from orange through various shades of green to a greenish blue. In fact, the color change observed with chromic acid can be used as a test for the presence of an oxidizable alcohol.

15-2B Oxidation of Primary Alcohols

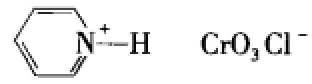
Oxidation of a primary alcohol initially forms an aldehyde. Unlike a ketone, however, an aldehyde is easily oxidized further to give a carboxylic acid.



Obtaining the aldehyde is often difficult, since most oxidizing agents strong enough to oxidize primary alcohols also oxidize aldehydes. Chromic acid generally oxidizes a primary alcohol all the way to the carboxylic acid.



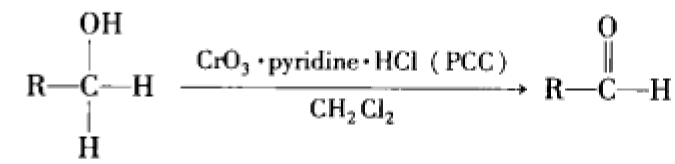
Pyridinium chlorochromate (PCC):
(氯铬酸吡啶鎓)



$CrO_3 \cdot pyridine \cdot HCl$

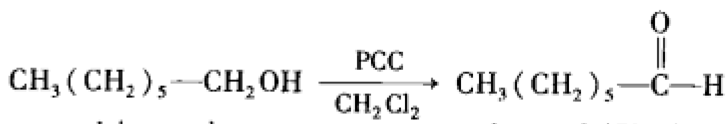
or $pyH^+ \ CrO_3Cl^-$

A better reagent for the limited oxidation of primary alcohols to aldehydes is **pyridinium chlorochromate (PCC)**, a complex of chromium trioxide with pyridine and HCl. PCC oxidizes most primary alcohols to aldehydes in excellent yields. Unlike most other oxidants, PCC is soluble in nonpolar solvents such as dichloromethane (CH_2Cl_2), which is an excellent solvent for most organic compounds. PCC can also serve as a mild reagent for oxidizing secondary alcohols to ketones.



primary alcohol aldehyde

Example



1-heptanol heptanal (78%)

15-2C Resistance of Tertiary Alcohols to Oxidation

Oxidation of tertiary alcohols is not an important reaction in organic chemistry. Tertiary alcohols have no hydrogen atoms on the carbinol carbon atom, so oxidation must take place by breaking carbon-carbon bonds. These oxidations require severe conditions and result in mixtures of products.

The **chromic acid test** for primary and secondary alcohols exploits the resistance of tertiary alcohols to oxidation. When a primary or secondary alcohol is added to the chromic acid reagent, the orange color changes to green or blue. When a nonoxidizable substance (such as a tertiary alcohol, a ketone, or an alkane) is added to the reagent, no immediate color change occurs.

Summary of Alcohol Oxidations

To Oxidize	Product	Reagent
2° alcohol	ketone	chromic acid (or PCC)
1° alcohol	aldehyde	PCC
1° alcohol	carboxylic acid	chromic acid

PROBLEM 15-1

Predict the products of the reactions of the following compounds with chromic acid and also with PCC.

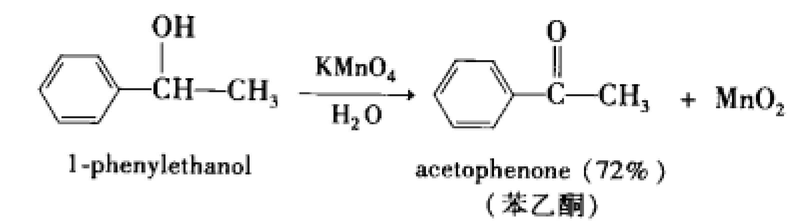
(a) cyclohexanol
(b) 1-methylcyclohexanol
(c) 2-methylcyclohexanol
(d) cyclohexanone
(e) cyclohexane
(f) acetic acid, CH_3COOH
(g) ethanol
(h) acetaldehyde, CH_3CHO

15-3 Additional Methods for Oxidizing Alcohols

Many other reagents and procedures have been developed for oxidizing alcohols. Some are simply modifications of

the procedures we have seen. For example, the **Collins reagent** is a complex of chromium trioxide and pyridine, the original version of PCC. The **Jones reagent** is a milder form of chromic acid: a solution of diluted chromic acid in acetone.

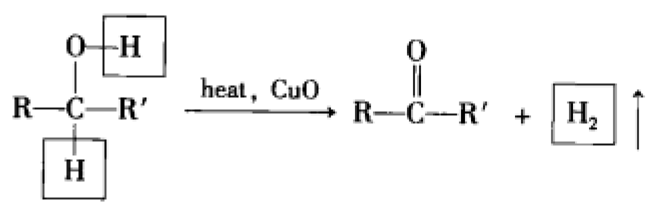
Two other strong oxidants are potassium permanganate and nitric acid. Both of these reagents are less expensive than the chromium reagents, and both of them give byproducts that are less environmentally hazardous than spent chromium reagents. Both permanganate and nitric acid oxidize secondary alcohols to ketones and primary alcohols to carboxylic acids. If these strong oxidants are not carefully controlled, they will cleave carbon-carbon bonds.



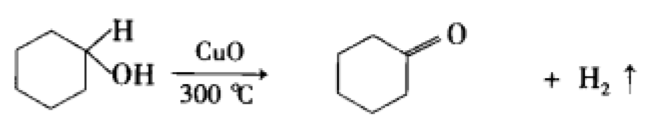
$$CH_3(CH_2)_4—CH_2OH \xrightarrow[10\ \text{to}\ 20\ ^\circ C]{71\%\ HNO_3} CH_3(CH_2)_4—\overset{O}{\overset{\|}{C}}—OH$$

1-hexanol hexanoic acid (80%)

Perhaps the least expensive method for oxidizing alcohols is dehydrogenation: literally the removal of two hydrogen atoms. This industrial reaction takes place at high temperature using a copper or copper oxide catalyst. The hydrogen byproduct may be sold or used for reductions elsewhere in the plant. The primary limitation of dehydrogenation is the inability of many organic compounds to survive a reaction at 300 ℃. *Dehydrogenation is not well suited for laboratory syntheses.*

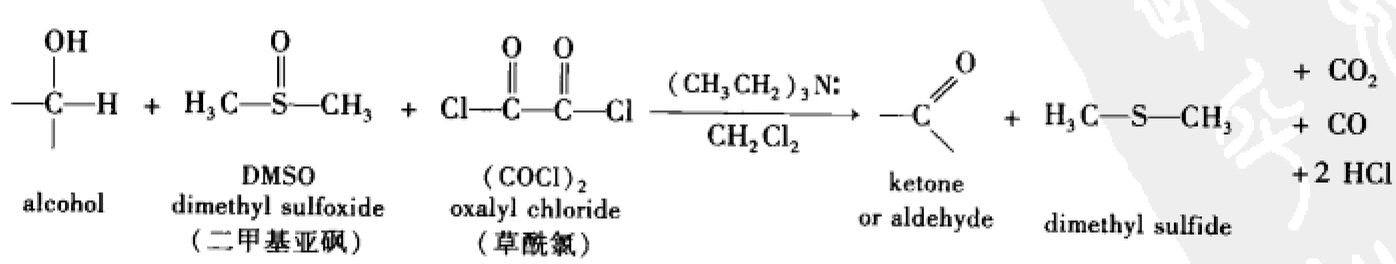


Example

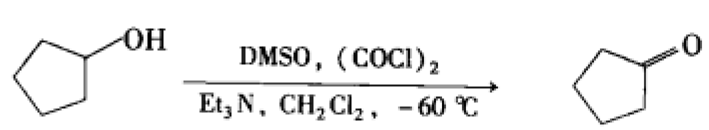


cyclohexanol cyclohexanone (90%)

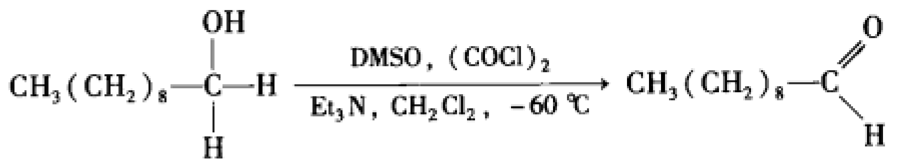
The **Swern oxidation** uses dimethyl sulfoxide (DMSO) as the oxidizing agent to convert alcohols to ketones and aldehydes. DMSO and oxalyl chloride are added to the alcohol at low temperature, followed by a hindered base such as triethylamine. Secondary alcohols are oxidized to ketones, and primary alcohols are oxidized only as far as the aldehyde. The byproducts of this reaction are all volatile and are easily separated from the organic products.



Examples



cyclopentanol cyclopentanone (90%)



1-decanol decanal (85%)

PROBLEM 15-2

The Swern oxidation provides a useful alternative to PCC that avoids using chromium reagents as oxidants.

(a) Determine which species are oxidized and which are reduced in the Swern oxidation.

(b) We have seen dimethyl sulfide before (Section 9-15B), added to an ozonide after ozonolysis. What was its function there?

PROBLEM 15-3

What is it about dehydrogenation that enables it to take place at 300 ℃ but not at 25 ℃?

(a) Would you expect the kinetics, thermodynamics, or both to be unfavorable at 25 ℃? (*Hint*: Is the reverse reaction favorable at 25 ℃?)

(b) Which of these factors (kinetics or thermodynamics) improves as the temperature is raised?

(c) Explain the changes in the kinetics and thermodynamics of this reaction as the temperature increases.

PROBLEM 15-4

Suggest the most appropriate method for each of the following *laboratory* syntheses.

(a) 1-butanol ⟶ butanal, $CH_3CH_2CH_2CHO$

(b) 1-butanol ⟶ butanoic acid, $CH_3CH_2CH_2COOH$

(c) 2-butanol ⟶ 2-butanone, $CH_3COCH_2CH_3$

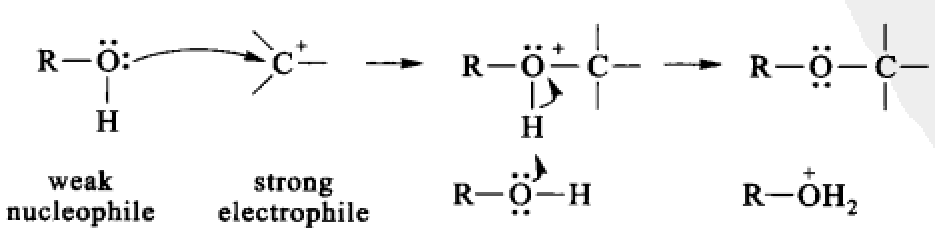
(d) 2-buten-1-ol ⟶ 2-butenal, $CH_3CH{=}CH{-}CHO$

(e) 2-buten-1-ol ⟶ 2-butenoic acid, $CH_3CH{-}CH{-}COOH$

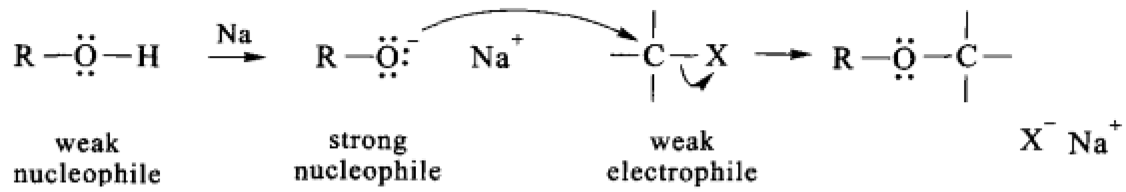
(f) 1-methylcyclohexanol ⟶ 2-methylcyclohexanone (several steps)

15-4 Alcohols as Nucleophiles and Electrophiles; Formation of Tosylates

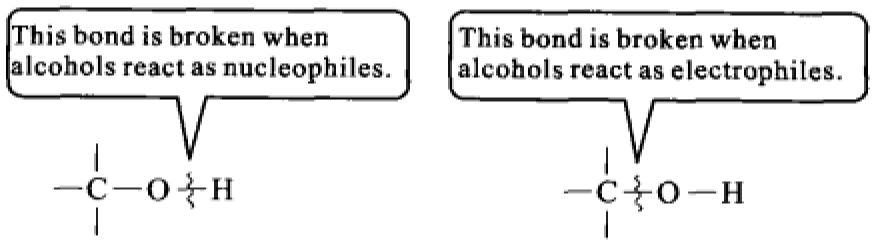
One reason alcohols are such versatile chemical intermediates is that they react as both nucleophiles and electrophiles. The following scheme shows an alcohol reacting as a weak nucleophile, bonding to a strong electrophile (in this case, a carbocation).



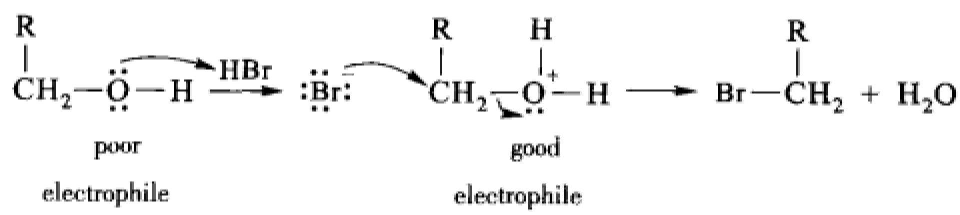
An alcohol is easily converted to a strong nucleophile by forming its alkoxide ion. The alkoxide ion can attack a weaker electrophile, such as an alkyl halide.



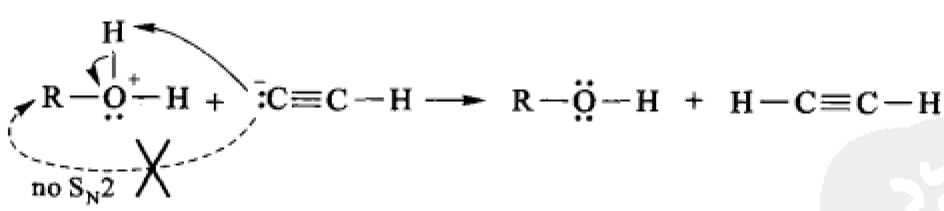
The O—H bond is broken when alcohols react as nucleophiles, both when an alcohol reacts as a weak nucleophile and when the alcohol is converted to its alkoxide that then reacts as a strong nucleophile. In contrast, when an alcohol reacts as an electrophile, the C—O bond is broken.



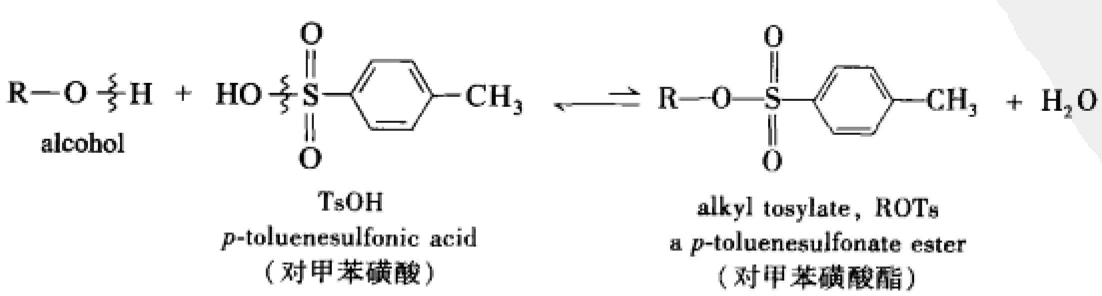
An alcohol is a weak electrophile because the hydroxyl group is a poor leaving group. The hydroxyl group becomes a good leaving group (H_2O) when it is protonated. For example, HBr reacts with a primary alcohol by an S_N2 attack of bromide on the protonated alcohol. Note that the C—O bond is broken in this reaction.



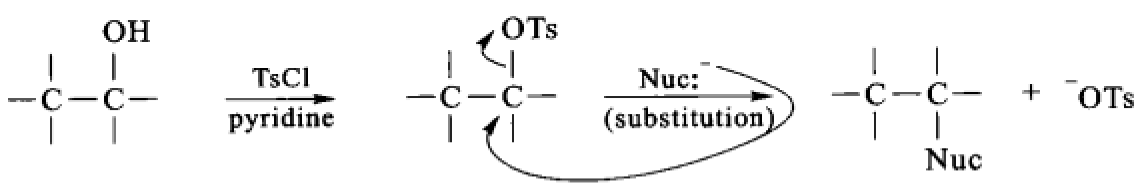
The disadvantage of using a protonated alcohol is that a strongly acidic solution is required to protonate the alcohol. Although halide ions are stable in acid, few other good nucleophiles are stable in strongly acidic solutions. Most strong nucleophiles are also basic and will abstract a proton in acid. Once protonated, the reagent is no longer nucleophilic. For example, an acetylide ion would instantly become protonated if it were added to a protonated alcohol.



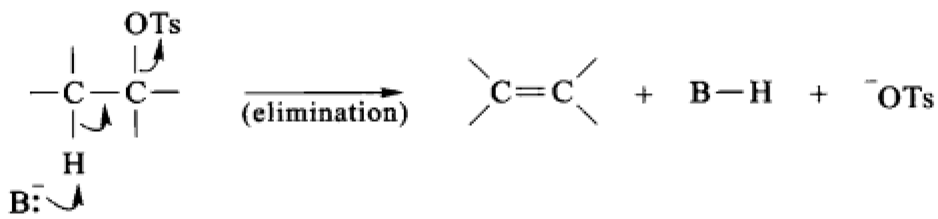
How can we convert an alcohol to an electrophile that is compatible with basic nucleophiles? We can convert it to an alkyl halide, or we can simply make its tosylate ester. A **tosylate ester** (symbolized ROTs) is the product of condensation of an alcohol with *p*-toluenesulfonic acid (symbolized TsOH).



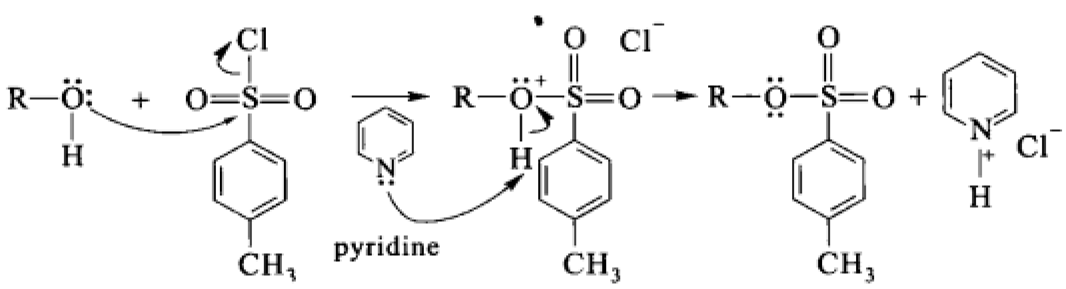
The tosylate group is an excellent leaving group, and alkyl tosylates undergo substitution and elimination much like alkyl halides. In many cases, a tosylate is more reactive than the equivalent alkyl halide.



or elimination:

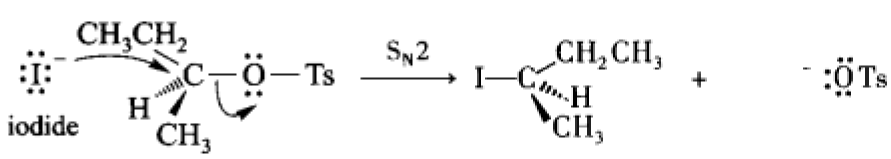


Tosylates are made from alcohols using tosyl chloride (TsCl) in pyridine, as shown next. This reaction gives much higher yields than the reaction with TsOH itself. The mechanism of tosylate formation shows that the C—O bond of the alcohol remains intact throughout the reaction, and the alcohol retains its stereochemical configuration. Pyridine serves as an organic base to remove the HCl formed in the reaction, preventing it from protonating the alcohol and causing side reactions.



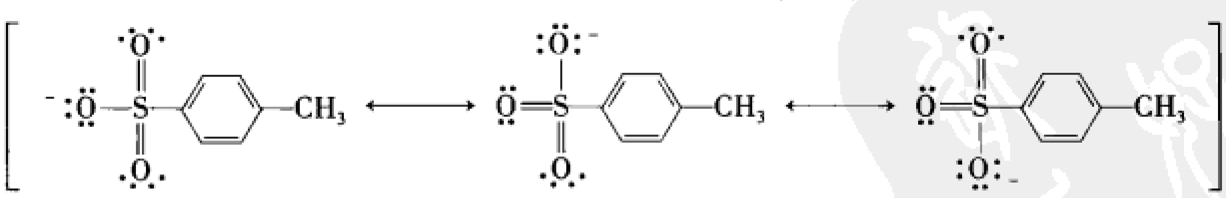
p-toluenesulfonyl chloride (对甲苯磺酰氯) TsCl, "tosyl chloride" ROTs, a tosylate ester

The following reaction shows the S_N2 displacement of tosylate ion (^-OTs) from (*S*)-2-butyl tosylate with inversion of configuration. The tosylate ion is a particularly stable anion, with its negative charge delocalized over three oxygen atoms.



(*S*)-2-butyl tosylate (*R*)-2-butyl iodide tosylate ion (甲苯磺酸根离子)

^-OTs tosylate ion =



resonance-stabilized anion

Like halides, the tosylate leaving group is displaced by a wide variety of nucleophiles. The S_N2 mechanism (strong nucleophile) is more commonly used than the S_N1 in synthetic preparations. The following reactions show the generality of S_N2 displacements of tosylates. In each case, R must be a primary or unhindered secondary alkyl group if substitution is to predominate over elimination.

SUMMARY S_N2 Reactions of Tosylate Esters

$$R\text{—}OTs + {}^-OH \longrightarrow R\text{—}OH + {}^-OTs$$

hydroxide alcohol

$$\underset{}{R{-}OTs} + \underset{\text{cyanide}}{{}^{-}C{\equiv}N} \longrightarrow \underset{\text{nitrile}}{R{-}C{\equiv}N} + {}^{-}OTs$$

$$R{-}OTs + \underset{\text{halide}}{Br^{-}} \longrightarrow \underset{\text{alkyl halide}}{R{-}Br} + {}^{-}OTs$$

$$R{-}OTs + \underset{\text{alkoxide}}{R'{-}O^{-}} \longrightarrow \underset{\text{ether}}{R{-}O{-}R'} + {}^{-}OTs$$

$$R{-}OTs + \underset{\text{ammonia}}{:NH_3} \longrightarrow \underset{\text{amine salt}}{R{-}NH_3^{+}\ {}^{-}OTs}$$

$$R{-}OTs + \underset{\text{LAH}}{LiAlH_4} \longrightarrow \underset{\text{alkane}}{R{-}H} + {}^{-}OTs$$

PROBLEM 15−5

Predict the major products of the following reactions.

(**a**) ethyl tosylate + potassium *t*-butoxide

(**b**) isobutyl tosylate + NaI

(**c**) (*R*)-2-hexyl tosylate + NaCN

(**d**) the tosylate of cyclohexylmethanol + excess NH_3

(**e**) *n*-butyl tosylate + sodium acetylide, $H{-}C{\equiv}C:^{-}\ {}^{+}Na$

PROBLEM 15−6

Show how you would convert 1-propanol (and whatever reagents are needed) to the following compounds using tosylate intermediates.

(**a**) 1-bromopropane

(**b**) *n*-propylamine, $CH_3CH_2CH_2NH_2$

(**c**) $CH_3CH_2CH_2OCH_2CH_3$ ethyl propyl ether

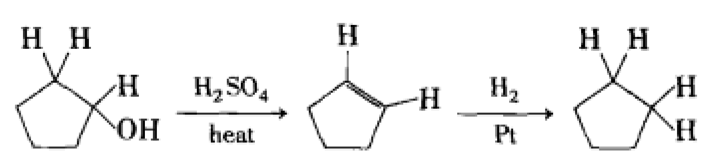
(**d**) $CH_3CH_2CH_2CN$ butyronitrile (丁腈)

15−5 Reduction of Alcohols

The reduction of alcohols to alkanes is not a common reaction because it removes a functional group, leaving fewer options for further reactions.

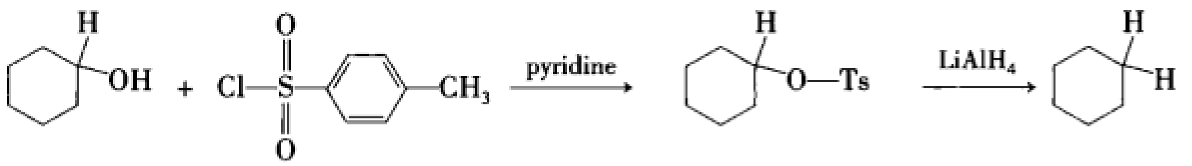
$$R{-}OH \xrightarrow{\text{reduction}} R{-}H \quad (\text{rare})$$

We can reduce an alcohol in two steps, by dehydrating it to an alkene, then hydrogenating the alkene.



cyclopentanol cyclopentene cyclopentane

Another method for reducing an alcohol involves converting the alcohol to the tosylate ester, then using a hydride reducing agent to displace the tosylate leaving group. This reaction works with most primary and secondary alcohols.

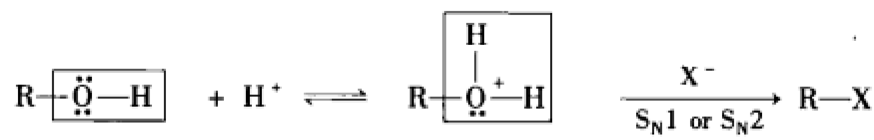


cyclohexanol tosyl chloride, TsCl cyclohexyl tosylate (对甲苯磺酸环己基酯) cyclohexane (75%)

15-6 Reactions of Alcohols with Hydrohalic Acids

Tosylation of an alcohol, followed by displacement of the tosylate by a halide ion, converts an alcohol to an alkyl halide. This is not the most common method for converting alcohols to alkyl halides, however, because simple, one-step reactions are available. A common method is to treat the alcohol with a hydrohalic acid, usually HCl or HBr.

In acidic solution, an alcohol is in equilibrium with its protonated form. Protonation converts the hydroxyl group from a poor leaving group (^-OH) to a good leaving group (H_2O). Once the alcohol is protonated, all the usual substitution and elimination reactions are feasible, depending on the structure (1°, 2°, 3°) of the alcohol.



poor leaving group good leaving group

Most good nucleophiles are basic, becoming protonated and losing their nucleophilicity in acidic solutions. Halide ions are exceptions, however. Halides are anions of strong acids, so they are weak bases. Solutions of HBr and HCl contain nucleophilic Br^- and Cl^- ions. These acids are commonly used to convert alcohols to the corresponding alkyl halides.

Reactions with Hydrobromic Acid

$$R{-}OH + HBr \longrightarrow R{-}Br + H_2O$$

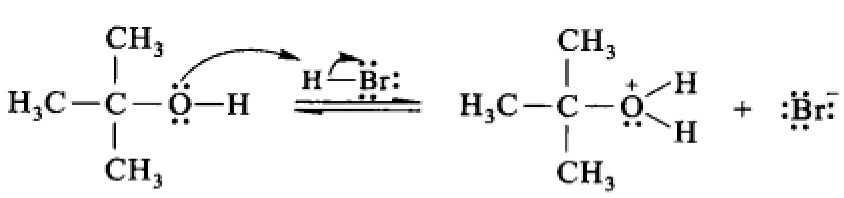
Concentrated hydrobromic acid rapidly converts *t*-butyl alcohol to *t*-butyl bromide. The strong acid protonates the hydroxyl group, converting it to a good leaving group. The hindered tertiary carbon atom cannot undergo S_N2 displacement, but it can ionize to a tertiary carbocation. Attack by bromide gives the alkyl bromide. The mechanism is similar to other S_N1 mechanisms we have studied, except that water serves as the leaving group from the protonated alcohol.

MECHANISM 15-1 Reaction of a Tertiary Alcohol with HBr (S_N1)

A tertiary alcohol reacts with HBr by the S_N1 mechanism.

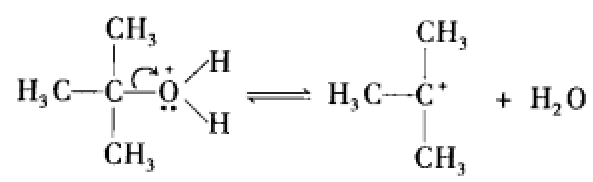
EXAMPLE: Conversion of *t*-butyl alcohol to *t*-butyl bromide.

Step 1: Protonation converts the hydroxyl group to a good leaving group.

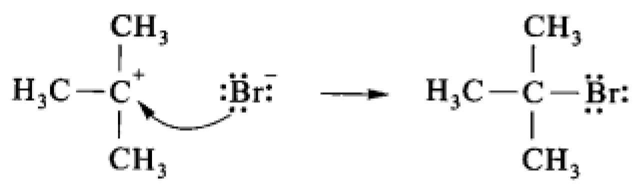


t-butyl alcohol

Step 2: Water leaves, forming a carbocation.



Step 3: Bromide ion attacks the carbocation.



t-butyl bromide

Many other alcohols react with HBr, with the reaction mechanism depending on the structure of the alcohol. For example, 1-butanol reacts with sodium bromide in concentrated sulfuric acid to give 1-bromobutane by an S_N2 displacement. The sodium bromide/sulfuric acid reagent generates HBr in the solution.

$$\underset{\text{1-butanol}}{CH_3(CH_2)_2—CH_2OH} \xrightarrow{NaBr,\ H_2SO_4} \underset{\text{1-bromobutane (90\%)}}{CH_3(CH_2)_2—CH_2Br}$$

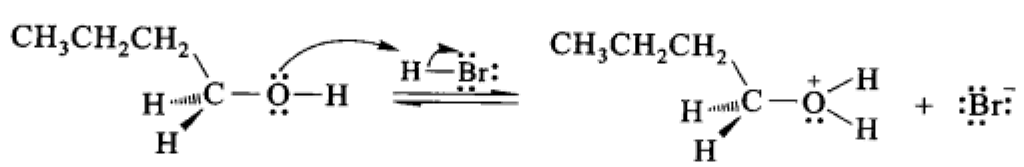
Protonation converts the hydroxyl group to a good leaving group, but ionization to a primary carbocation is unfavorable. The protonated primary alcohol is well suited for the S_N2 displacement, however. Back-side attack by bromide ion gives 1-bromobutane.

MECHANISM 15-2 Reaction of a Primary Alcohol with HBr (S_N2)

A primary alcohol reacts with HBr by the S_N2 mechanism.

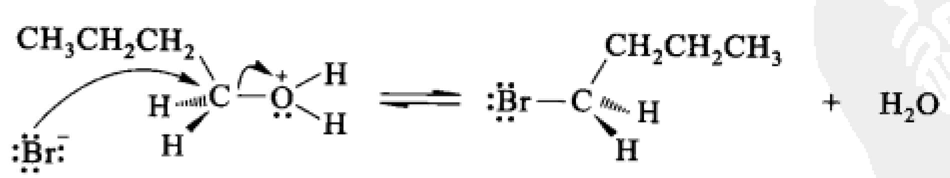
EXAMPLE: Conversion of 1-butanol to 1-bromobutane.

Step 1: Protonation converts the hydroxyl group to a good leaving group.



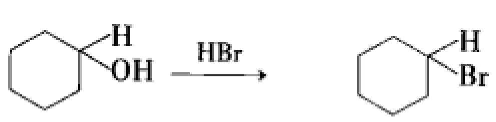
1-butanol

Step 2: Bromide displaces water to give the alkylbromide.



1-bromobutane

Secondary alcohols also react with HBr to form alkyl bromides, usually by the S_N1 mechanism. For example, cyclohexanol is converted to bromocyclohexane using HBr as the reagent.



cyclohexanol bromocyclohexane (80%)

PROBLEM 15-7

Propose a mechanism for the reaction of

(a) cyclohexanol with HBr to form bromocyclohexane.

(b) 2-cyclohexylethanol with HBr to form 1-bromo-2-cyclohexylethane.

Reactions with Hydrochloric Acid

$$R\text{—}OH + HCl/H_2O \xrightarrow{ZnCl_2} R\text{—}Cl$$

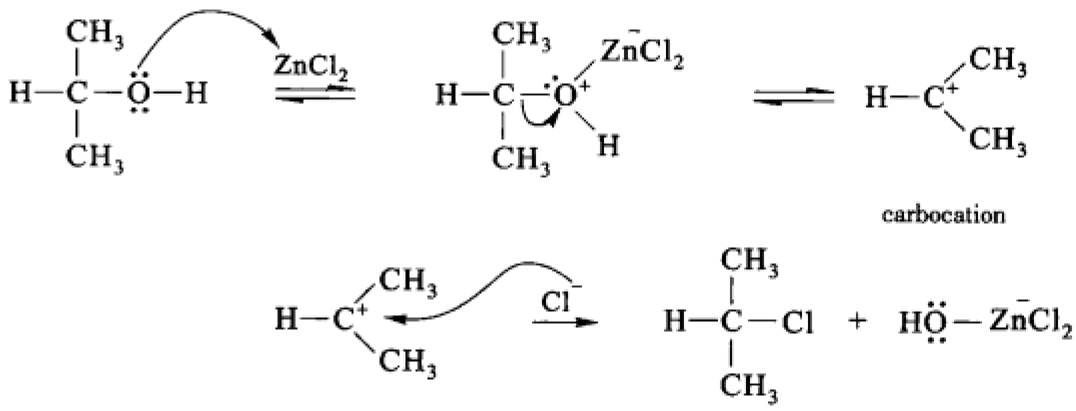
Hydrochloric acid (HCl) reacts with alcohols in much the same way that hydrobromic acid does. For example, concentrated aqueous HCl reacts with *t*-butyl alcohol to give *t*-butyl chloride.

$$\underset{t\text{-butyl alcohol}}{(CH_3)_3C\text{—}OH} + HCl/H_2O \longrightarrow \underset{t\text{-butyl chloride (98\%)}}{(CH_3)_3C\text{—}Cl} + H_2O$$

Chloride ion is a weaker nucleophile than bromide ion because it is smaller and less polarizable. An additional Lewis acid, such as zinc chloride ($ZnCl_2$), is sometimes necessary to promote the reaction of HCl with primary and secondary alcohols. Zinc chloride coordinates with the oxygen of the alcohol in the same way a proton does—except that zinc chloride coordinates more strongly.

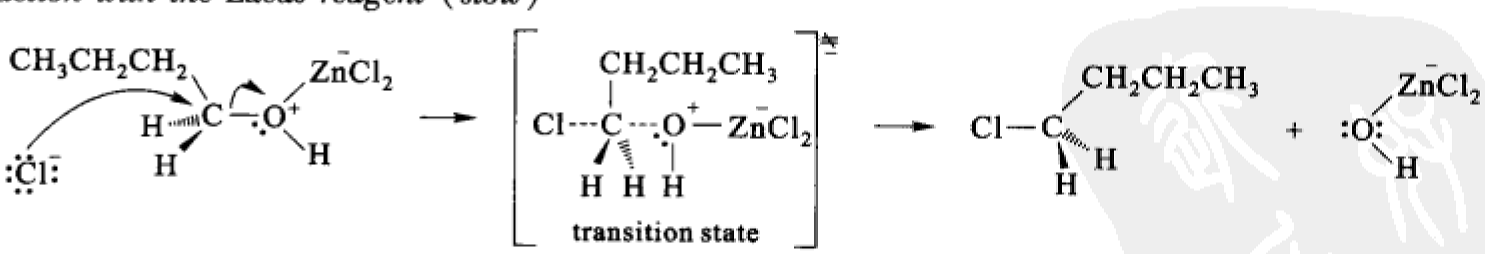
The reagent composed of HCl and $ZnCl_2$ is called the **Lucas reagent**. Secondary and tertiary alcohols react with the Lucas reagent by the S_N1 mechanism.

S_N1 reaction with the Lucas reagent (fast)



When a primary alcohol reacts with the Lucas reagent, ionization is not possible—the primary carbocation is too unstable. Primary substrates react by an S_N2 mechanism, which is slower than the S_N1 reaction of secondary and tertiary substrates. For example, when 1-butanol reacts with the Lucas reagent, the chloride ion attacks the complex from the back, displacing the leaving group.

S_N2 reaction with the Lucas reagent (slow)



The Lucas Test The Lucas reagent reacts with primary, secondary, and tertiary alcohols at fairly predictable rates, and these rates can be used to distinguish among the three types of alcohols. When the reagent is first added to the alcohol, the mixture forms a single homogeneous phase: The concentrated HCl solution is very polar, and the polar alcohol-zinc chloride complex dissolves. Once the alcohol has reacted to form the alkyl halide, the relatively nonpolar halide separates into a second phase.

The **Lucas test** involves adding the Lucas reagent to an unknown alcohol and watching for the second phase to separate (see Table 15-1). Tertiary alcohols react almost instantaneously because they form relatively stable

tertiary carbocations. Secondary alcohols react in about 1 to 5 minutes because their secondary carbocations are less stable than tertiary ones. Primary alcohols react very slowly. Since the activated primary alcohol cannot form a carbocation, it simply remains in solution until it is attacked by the chloride ion. With a primary alcohol, the reaction may take from 10 minutes to several days.

TABLE 15-1 Reactions of Alcohols with the Lucas Reagent

Alcohol Type	Time to React/min
primary	>6
secondary	1−5
tertiary	<1

PROBLEM 15−8

Show how you would use a simple chemical test to distinguish between the following pairs of compounds. Tell what you would observe with each compound.

(a) isopropyl alcohol and *t*-butyl alcohol
(b) isopropyl alcohol and 2-butanone, $CH_3COCH_2CH_3$
(c) 1-hexanol and cyclohexanol
(d) allyl alcohol and 1-propanol
(e) 2-butanone and *t*-butyl alcohol

Limitations on the Use of Hydrohalic Acids with Alcohols The reactions of alcohols with hydrohalic acids do not always give good yields of the expected alkyl halides. Four principal limitations restrict the generality of this technique.

1. *Poor yields of alkyl chlorides from primary and secondary alcohols.* Primary and secondary alcohols react with HCl much more slowly than tertiary alcohols, even with zinc chloride added. Under these conditions, side reactions prevent good yields of the alkyl halides.

2. *Eliminations.* Heating an alcohol in a concentrated acid such as HCl or HBr often leads to elimination. Once the hydroxyl group of the alcohol has been protonated and converted to a good leaving group, it becomes a candidate for both substitution and elimination.

3. *Rearrangements.* Carbocation intermediates are always prone to rearrangements. We have seen (Section 7−14) that hydrogen atoms and alkyl groups can migrate from one carbon atom to another to form a more stable carbocation. This rearrangement may occur as the leaving group leaves, or it may occur once the cation has formed.

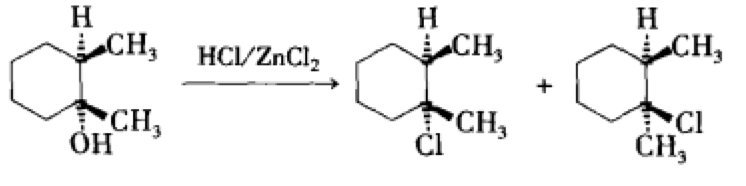
4. *Limited ability to make alkyl iodides.* Many alcohols do not react with HI to give acceptable yields of alkyl iodides. Alkyl iodides are valuable intermediates, however, because iodides are the most reactive of the alkyl halides. We will discuss another technique for making alkyl iodides in the next section.

PROBLEM 15−9

Neopentyl alcohol, $(CH_3)_3CCH_2OH$, reacts with concentrated HBr to give 2-bromo-2-methylbutane, a rearranged product. Propose a mechanism for the formation of this product.

PROBLEM 15−10

Explain the products observed in the following reaction of an alcohol with the Lucas reagent.



PROBLEM 15−11

When *cis*-2-methylcyclohexanol reacts with the Lucas reagent, the major product is 1-chloro-1-methylcyclohexane. Propose a mechanism to explain the formation of this product.

15-7 Reactions of Alcohols with Phosphorus Halides

Several phosphorus halides are useful for converting alcohols to alkyl halides. Phosphorus tribromide, phosphorus trichloride, and phosphorus pentachloride work well and are commercially available.

$$3R—OH + PCl_3 \longrightarrow 3R—Cl + P(OH)_3$$

$$3R—OH + PBr_3 \longrightarrow 3R—Br + P(OH)_3$$

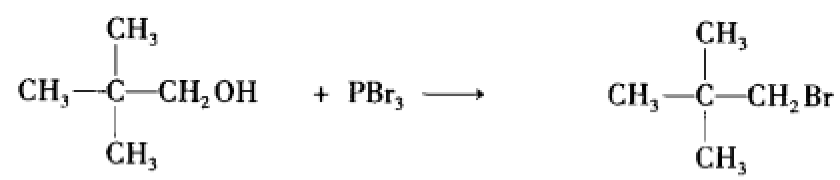
$$R—OH + PCl_5 \longrightarrow R—Cl + POCl_3 + HCl$$

Phosphorus triiodide is not sufficiently stable to be stored, but it can be generated in situ (in the reaction mixture) by the reaction of phosphorus with iodine.

$$6\ R—OH + 2\ P + 3\ I_2 \longrightarrow 6\ R—I + 2\ P(OH)_3$$

Phosphorus halides produce good yields of most primary and secondary alkyl halides, but none works well with tertiary alcohols. The two phosphorus halides used most often are PBr_3 and the phosphorus/iodine combination. Phosphorus tribromide is often the best reagent for converting a primary or secondary alcohol to the alkyl bromide, especially if the alcohol might rearrange in strong acid. A phosphorus and iodine combination is one of the best reagents for converting a primary or secondary alcohol to the alkyl iodide. For the synthesis of alkyl chlorides, thionyl chloride (discussed in the next section) generally gives better yields than PCl_3 or PCl_5, especially with tertiary alcohols.

The following examples show the conversion of primary and secondary alcohols to bromides and iodides by treatment with PBr_3 and P/I_2.



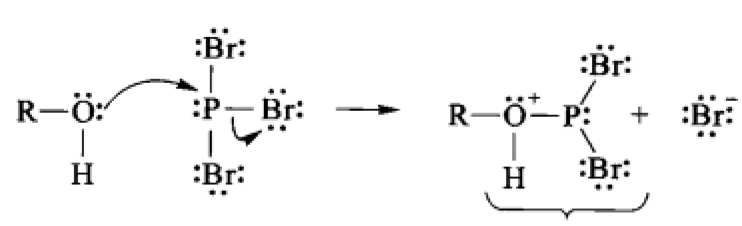
neopentyl alcohol (新戊醇) neopentyl bromide (新戊基溴) (60%)

$$CH_3(CH_2)_{14}—CH_2OH + P/I_2 \longrightarrow CH_3(CH_2)_{14}—CH_2I \quad (85\%)$$

Mechanism of the Reaction with Phosphorus Trihalides The mechanism of the reaction of alcohols with phosphorus trihalides explains why rearrangements are uncommon and why phosphorus halides work poorly with tertiary alcohols. The mechanism is shown here using PBr_3 as the reagent; PCl_3 and PI_3 (generated from phosphorus and iodine) react in a similar manner.

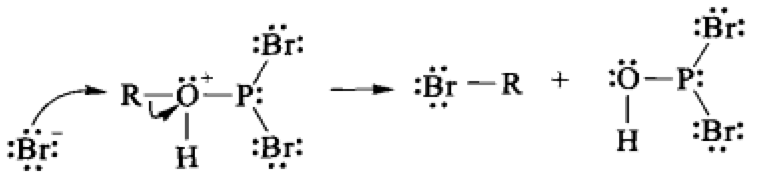
MECHANISM 15-3 Reaction of Alcohols with PBr_3

Step 1: PBr_3 is a strong electrophile. An alcohol displaces bromide ion from PBr_3 to give an excellent leaving group.



excellent leaving group

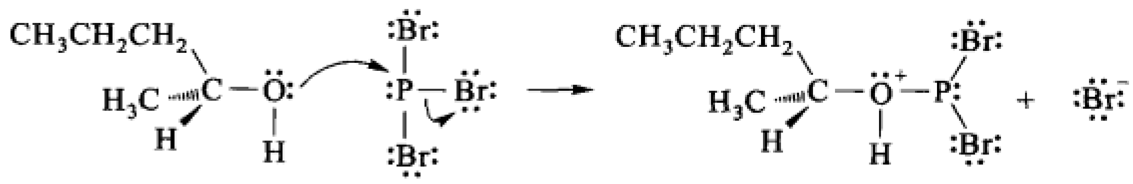
Step 2: Bromide displaces the leaving group to give the alkyl bromide.



leaving group

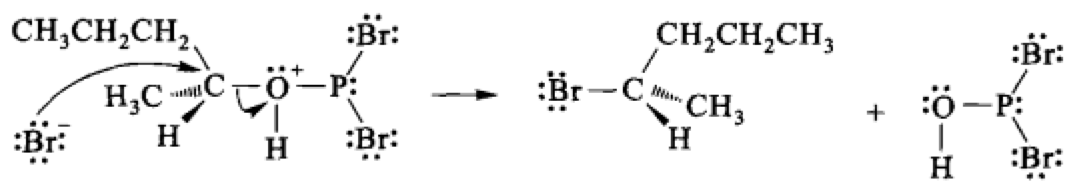
Example: **Reaction of (*R*)-2-pentanol with PBr_3.**

Step 1: Displacement of bromide and formation of a leaving group.



(*R*)-2-pentanol

Step 2: Bromide displaces the leaving group to give (*S*)-2-bromopentane.



(*S*)-2-bromopentane

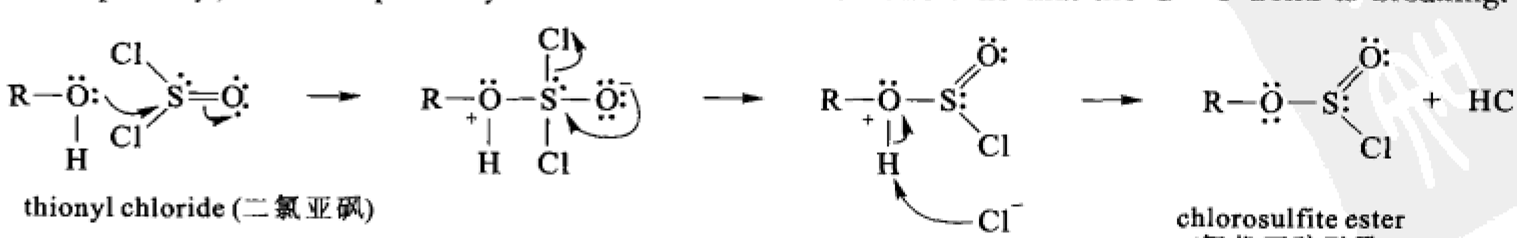
Rearrangements are uncommon because no carbocation is involved, so there is no opportunity for rearrangement. This mechanism also explains the poor yields with tertiary alcohols. The final step is an S_N2 displacement where bromide attacks the back side of the alkyl group. This attack is hindered if the alkyl group is tertiary. In the case of a tertiary alcohol, an ionization to a carbocation is needed. This ionization is slow, and it invites side reactions.

15−8 Reactions of Alcohols with Thionyl Chloride

Thionyl chloride ($SOCl_2$) is often the best reagent for converting an alcohol to an alkyl chloride. The byproducts (gaseous SO_2 and HCl) leave the reaction mixture and ensure there can be no reverse reaction.

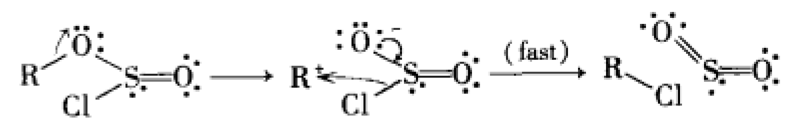
$$R{-}OH + Cl{-}\overset{\overset{\displaystyle O}{\|}}{S}{-}Cl \xrightarrow{\text{heat}} R{-}Cl + SO_2 + HCl$$

Under the proper conditions, thionyl chloride reacts by the interesting mechanism summarized next. In the first step, the nonbonding electrons of the hydroxyl oxygen atom attack the electrophilic sulfur atom of thionyl chloride. A chloride ion is expelled, and a proton is lost to give a chlorosulfite ester. In the next step, the chlorosulfite ester ionizes (when R = 2° or 3°), and the sulfur atom quickly delivers chloride to the carbocation. When R is primary, chloride probably bonds to carbon at the same time that the C—O bond is breaking.

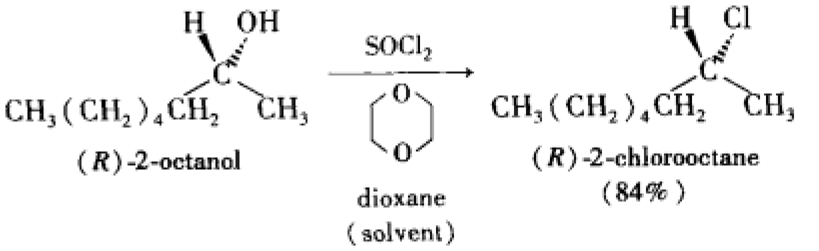


thionyl chloride (二氯亚砜)

chlorosulfite ester
(氯代亚硫酸酯)



This mechanism resembles the S_N1, except that the nucleophile is delivered to the carbocation by the leaving group, giving retention of configuration as shown in the following example. (Under different conditions, retention of configuration may not be observed.)



Summary of the Best Reagents for Converting Alcohols to Alkyl Halides

Class of Alcohol	Chloride	Bromide	Iodide
primary	$SOCl_2$	PBr_3 or HBr*	P/I_2
secondary	$SOCl_2$	PBr_3	P/I_2*
tertiary	HCl	HBr	HI*

* Works only in selected cases.

PROBLEM 15-12

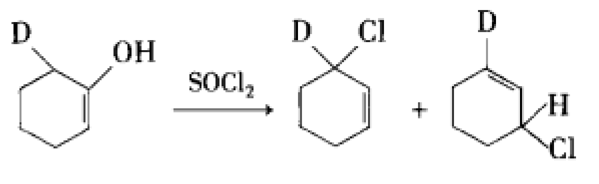
Suggest how you would convert *trans*-4-methylcyclohexanol to

(a) *trans*-1-chloro-4-methylcyclohexane.

(b) *cis*-1-chloro-4-methylcyclohexane.

PROBLEM 15-13

Two products are observed in the following reaction.



(a) Suggest a mechanism to explain how these two products are formed.

(b) Your mechanism for part (a) should be different from the usual mechanism of the reaction of $SOCl_2$ with alcohols. Explain why the reaction follows a different mechanism in this case.

PROBLEM 15-14

Give the structures of the products you would expect when each alcohol reacts with (1) HCl, $ZnCl_2$; (2) HBr; (3) PBr_3; (4) P/I_2; (5) $SOCl_2$.

(a) 1-butanol **(b)** 2-butanol **(c)** 2-methyl-2-butanol

(d) 2,2-dimethyl-1-butanol **(e)** *cis*-3-methylcyclopentanol

15-9 Dehydration Reactions of Alcohols

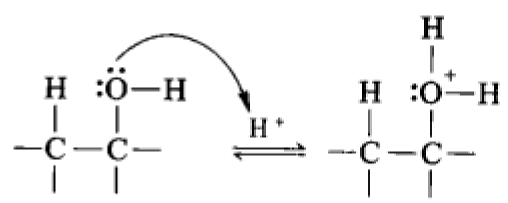
15-9A Formation of Alkenes

We studied the mechanism for dehydration of alcohols to alkenes in Section 7-10 together with other syntheses of alkenes. Dehydration requires an acidic catalyst to protonate the hydroxyl group of the alcohol and convert it to a good leaving group. Loss of water, followed by loss of a proton, gives the alkene. An equilibrium is established between reactants and products.

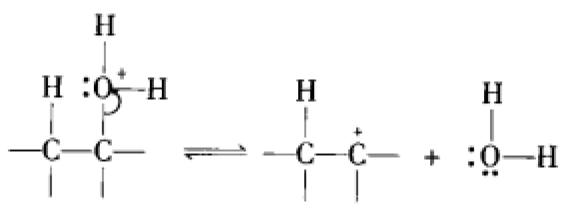
MECHANISM 15-4 (Review): Acid-Catalyzed Dehydration of an Alcohol

Dehydration results from E1 elimination of the protonated alcohol

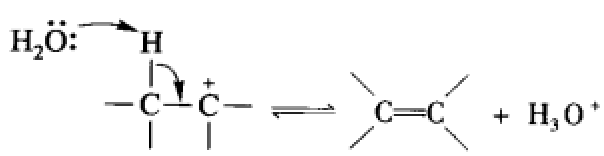
Step 1: Protonation converts the hydroxyl group to a good leaving group.



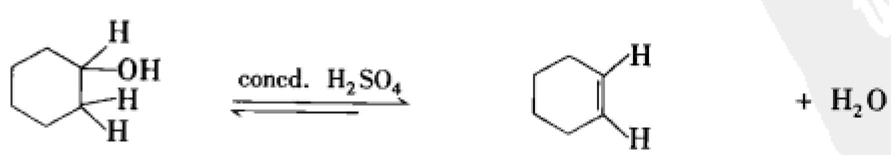
Step 2: Water leaves, forming a carbocation.



Step 3: Loss of a proton gives the alkene.

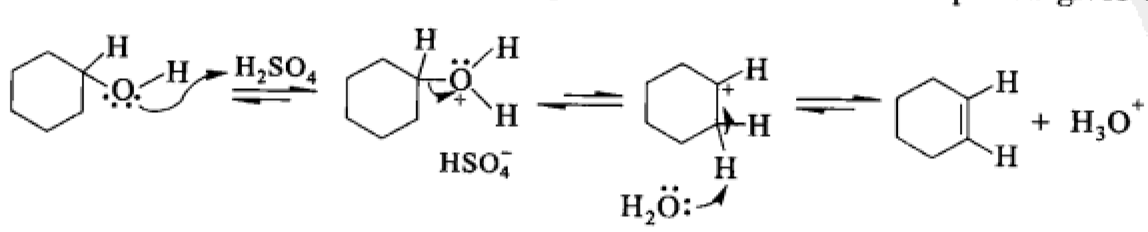


To drive this equilibrium to the right, we remove one or both of the products as they form, either by distilling the products out of the reaction mixture or by adding a dehydrating agent to remove water. In practice, we often use a combination of distillation and a dehydrating agent. The alcohol is mixed with a dehydrating acid, and the mixture is heated to boiling. The alkene boils at a lower temperature than the alcohol (because the alcohol is hydrogen-bonded), and the alkene distills out of the mixture. For example,



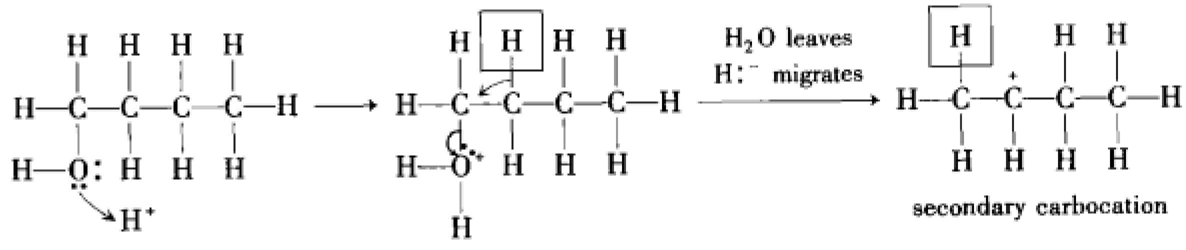
cyclohexanol, bp 161 ℃ — cyclohexene, bp 83 ℃ (80%) (distilled from the mixture)

Alcohol dehydrations generally take place through the E1 mechanism. Protonation of the hydroxyl group converts it to a good leaving group. Water leaves, forming a carbocation. Loss of a proton gives the alkene.

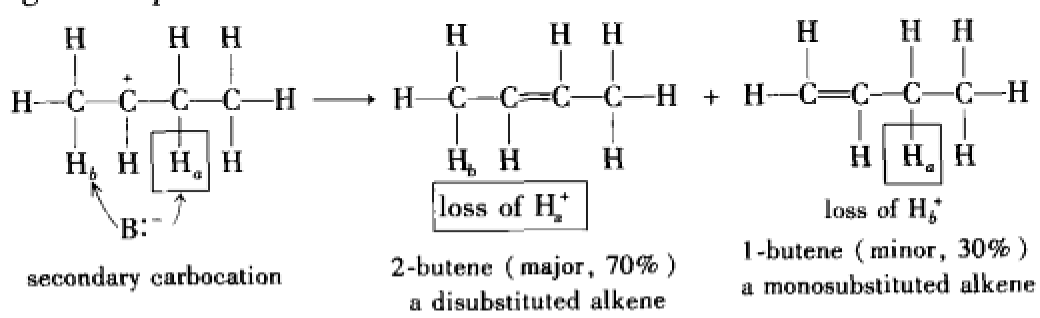


With primary alcohols, rearrangement and isomerization of the products are so common that acid-catalyzed dehydration is rarely a good method for converting them to alkenes. The following mechanism shows how 1-butanol undergoes dehydration with rearrangement to give a mixture of 1-butene and 2-butene. The more highly substituted product, 2-butene, is the major product, in accordance with the Zaitsev rule (Section 7-18).

Ionization of the protonated alcohol, with rearrangement



Loss of either proton to give two products



Let's review the utility of dehydration and give guidelines for predicting the products:

1. Dehydration usually goes by the E1 mechanism. Rearrangements may occur to form more stable carbocations.

2. Dehydration works best with tertiary alcohols and almost as well with secondary alcohols. Rearrangements and poor yields are common with primary alcohols.

3. (Zaitsev's rule) If two or more alkenes might be formed by deprotonation of the carbocation, the most highly substituted alkene usually predominates.

Solved Problem 15-1 shows how these rules are used to predict the products of dehydrations. The carbocations are drawn to show how rearrangements occur and how more than one product may result.

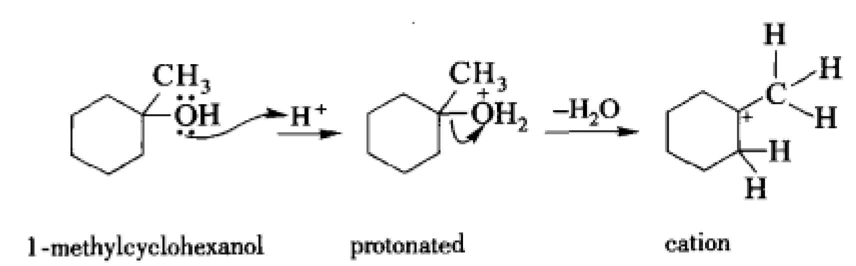
SOLVED PROBLEM 15-1

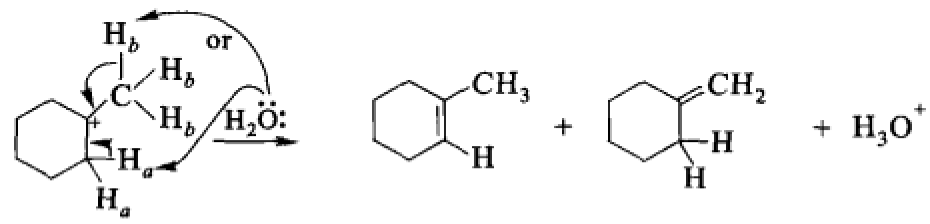
Predict the products of sulfuric acid-catalyzed dehydration of the following alcohols.

(a) 1-methylcyclohexanol **(b)** neopentyl alcohol

SOLUTION

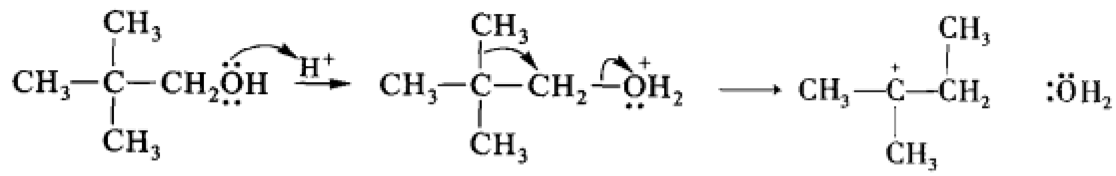
(a) 1-Methylcyclohexanol reacts to form a tertiary carbocation. A proton may be abstracted from any one of three carbon atoms. The two secondary atoms are equivalent, and abstraction of a proton from one of these carbons leads to the trisubstituted double bond of the major product. Abstraction of a methyl proton leads to the disubstituted double bond of the minor product.



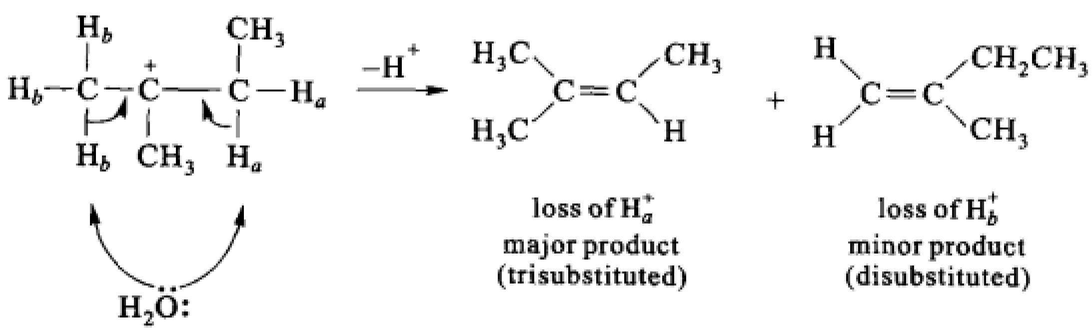


cation — loss of H_a, major product (trisubstituted) — loss of H_b, minor product (disubstituted)

(b) Neopentyl alcohol cannot simply ionize to form a primary cation. Rearrangement occurs as the leaving group leaves, giving a tertiary carbocation. Loss of a proton from the adjacent secondary carbon gives the trisubstituted double bond of the major product. Loss of a proton from the methyl group gives the disubstituted double bond of the minor product.



neopentyl alcohol (2,2-dimethyl-1-propanol) — ionization with rearrangement — 3° cation



loss of H_a^+, major product (trisubstituted) — loss of H_b^+, minor product (disubstituted)

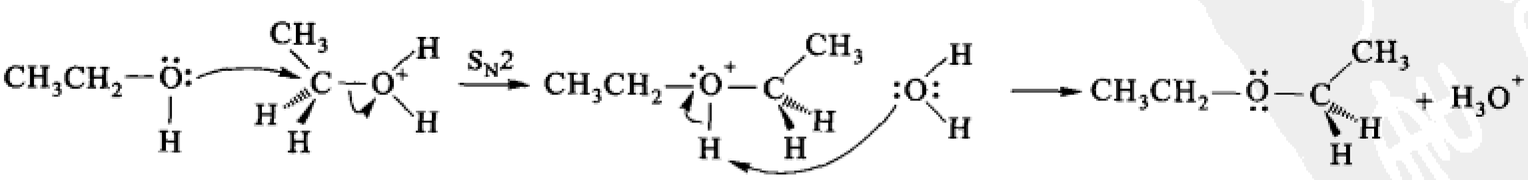
PROBLEM 15-15

Predict the products of the sulfuric acid-catalyzed dehydration of the following alcohols. When more than one product is expected, label the major and minor products.

(a) 2-methyl-2-butanol **(b)** 1-pentanol **(c)** 2-pentanol
(d) 1-isopropylcyclohexanol **(e)** 2-methylcyclohexanol

15-9B Bimolecular Dehydration to Form Ethers (Industrial)

In some cases, a protonated primary alcohol may be attacked by another molecule of the alcohol and undergo an S_N2 displacement. The net reaction is a bimolecular dehydration to form an ether. For example, the attack by ethanol on a protonated molecule of ethanol gives diethyl ether.



nucleophilic — electrophilic — protonated ether (质子化乙醚) — water — diethyl ether

Bimolecular dehydration can be used to synthesize symmetrical dialkyl ethers from simple, unhindered primary alcohols. This method is used for the industrial synthesis of diethyl ether (CH_3CH_2—O—CH_2CH_3) and

dimethyl ether ($CH_3—O—CH_3$). Under the acidic dehydration conditions, two reactions compete: Elimination (to give an alkene) competes with substitution (to give an ether).

Substitution to give the ether, a bimolecular dehydration

$$\underset{\text{ethanol}}{2\ CH_3CH_2OH} \xrightarrow{H_2SO_4,\ 140\ ℃} \underset{\text{diethyl ether}}{CH_3CH_2—O—CH_2CH_3} + H_2O$$

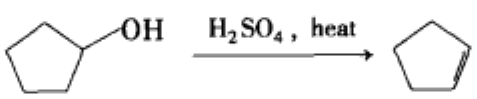
Elimination to give the alkene, a unimolecular dehydration

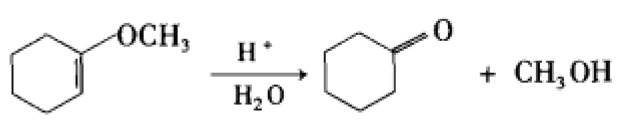
$$\underset{\text{ethanol}}{CH_3CH_2OH} \xrightarrow{H_2SO_4,\ 180°} \underset{\text{ethylene}}{CH_2{=}CH_2} + H_2O$$

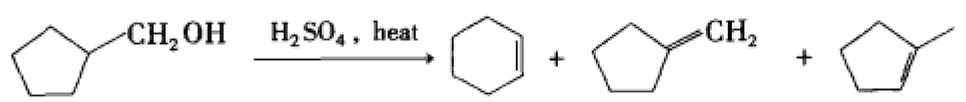
How can we control these two competing dehydrations? The ether synthesis (substitution) shows two molecules of alcohol giving two product molecules: one of diethyl ether and one of water. The elimination shows one molecule of alcohol giving two molecules: one of ethylene and one of water. The elimination results in an increase in the number of molecules and therefore an *increase* in the randomness (entropy) of the system. The elimination has a more positive change in entropy (ΔS) than the substitution, and the $-T\Delta S$ term in the Gibbs free energy becomes more favorable for the elimination as the temperature increases. Substitution (to give the ether) is favored around 140 ℃ and below, and elimination is favored around 180 ℃ and above. Diethyl ether is produced industrially by heating ethanol with an acidic catalyst at around 140 ℃.

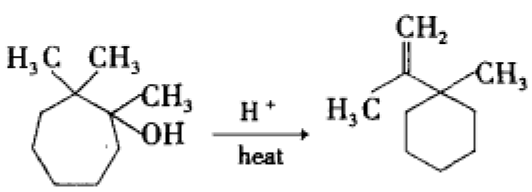
PROBLEM 15-16

Propose a mechanism for each reaction.

(a) 

(b) 

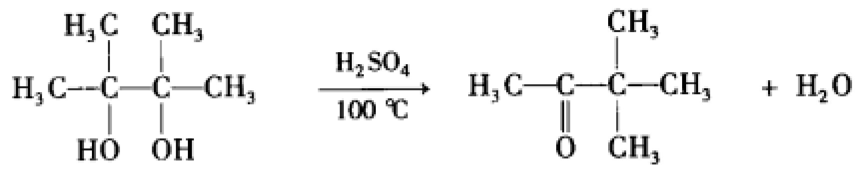
(c) 

(d) 

15-10 Unique Reactions of Diols

15-10A The Pinacol Rearrangement

Using our knowledge of alcohol reactions, we can explain results that seem strange at first glance. The following dehydration is an example of the **pinacol rearrangement**:



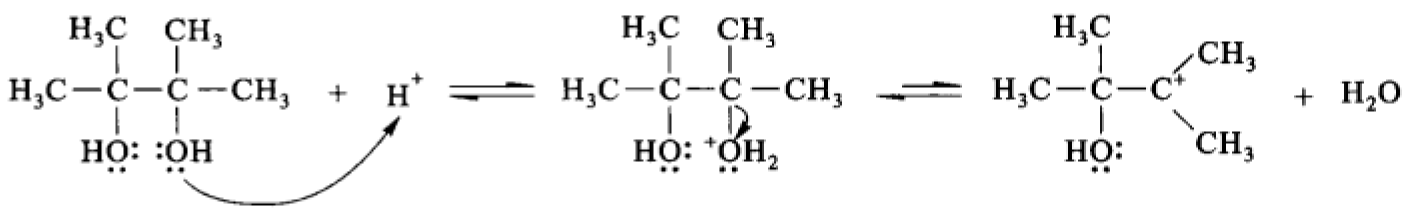
pinacol (频哪醇) (2,3-dimethyl-2,3-butanediol) — pinacolone (频哪酮) (3,3-dimethyl-2-butanone)

The pinacol rearrangement is formally a dehydration. The reaction is acidcatalyzed, and the first step is protonation of one of the hydroxyl oxygens. Loss of water gives a tertiary carbocation, as expected for any tertiary alcohol. Migration of a methyl group places the positive charge on the carbon atom bearing the second —OH group, where oxygen's nonbonding electrons help to stabilize the charge through resonance. This extra stability is the driving force for the rearrangement. Deprotonation of the resonance-stabilized cation gives the product, pinacolone.

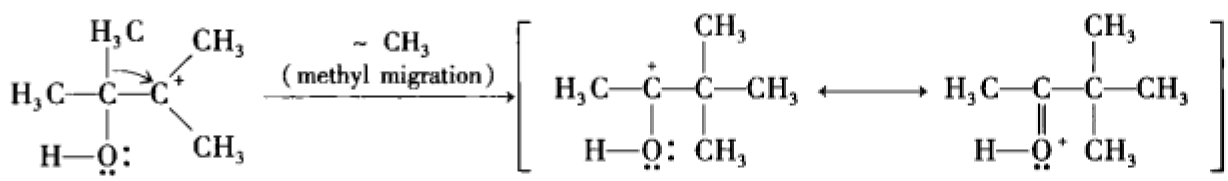
MECHANISM 15-5 The Pinacol Rearrangement

***Step 1*:** Protonation of a hydroxyl group.

***Step 2*:** Loss of water gives a carbocation.

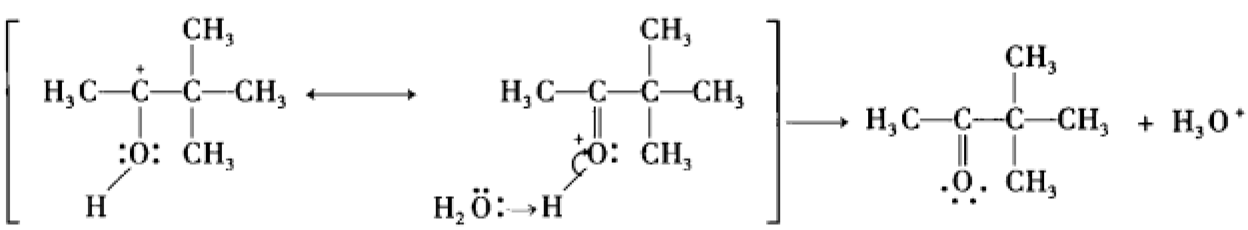


***Step 3*:** Methyl migration forms a resonance-stabilized carbocation.



resonance-stabilized carbocation

***Step 4*:** Deprotonation gives the product.



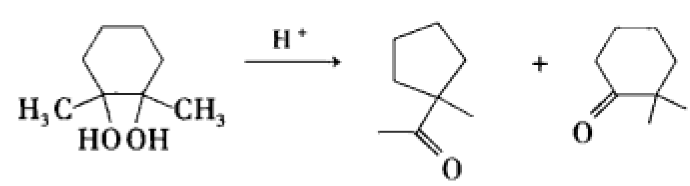
resonance-stabilized carbocation — pinacolone

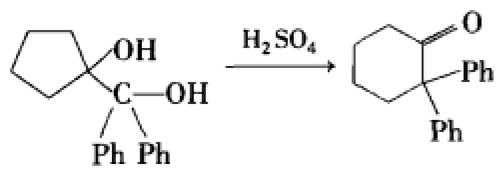
Pinacol-like rearrangements are common in acid-catalyzed reactions of diols. One of the hydroxyl groups protonates and leaves as water, forming a carbocation. Rearrangement gives a resonance-stabilized cation with the remaining hydroxyl group helping to stabilize the positive charge. Problem 15-17 shows some additional examples of pinacol rearrangements.

PROBLEM 15-17

Propose a mechanism for each reaction.

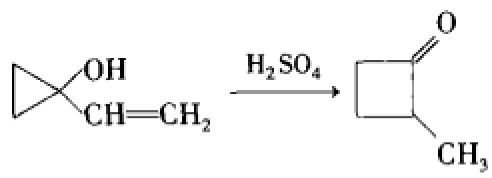
(a)



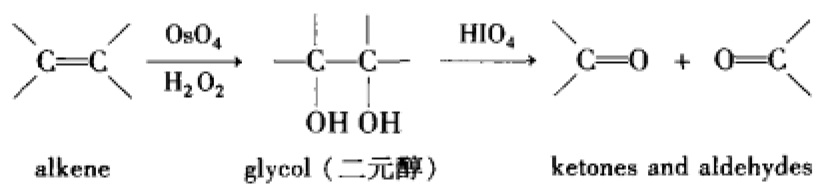
(b) 

PROBLEM 15-18

The following reaction involves a starting material with a double bond and a hydroxyl group, yet its mechanism resembles a pinacol rearrangement. Propose a mechanism, and point out the part of your mechanism that resembles a pinacol rearrangement.

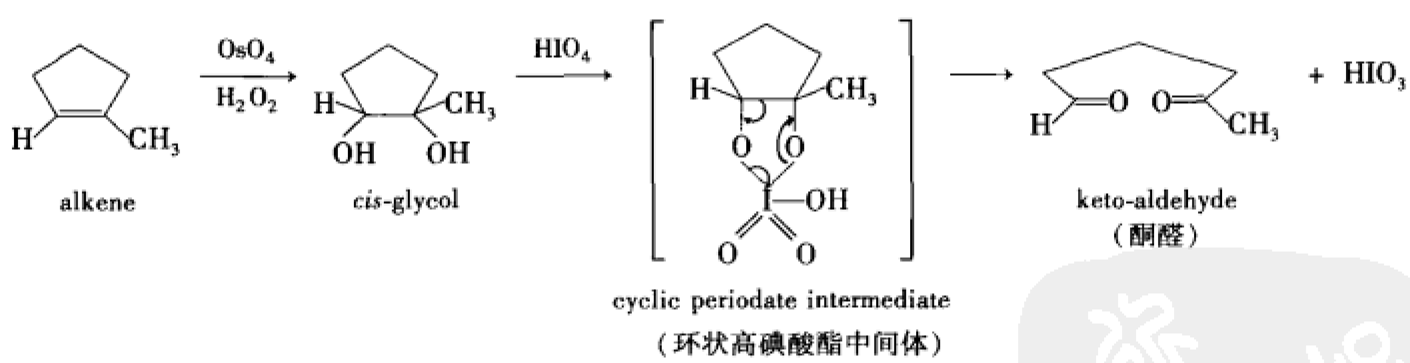


15-10B Periodic Acid Cleavage of Glycols



1,2-Diols (glycols), such as those formed by hydroxylation of alkenes, are cleaved by periodic acid (HIO_4). The products are the same ketones and aldehydes that would be formed by ozonolysis-reduction of the alkene. Hydroxylation followed by periodic acid cleavage serves as a useful alternative to ozonolysis, and the periodate cleavage by itself is useful for determining the structures of sugars (Chapter 24).

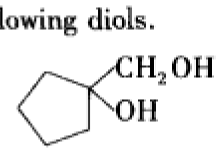
Periodic acid cleavage of a glycol probably involves a cyclic periodate intermediate like that shown here.

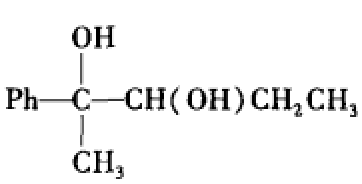


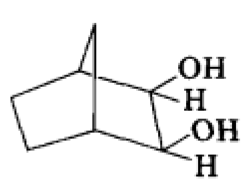
PROBLEM 15-19

Predict the products formed by periodic acid cleavage of the following diols.

(a) $CH_3CH(OH)CH(OH)CH_3$

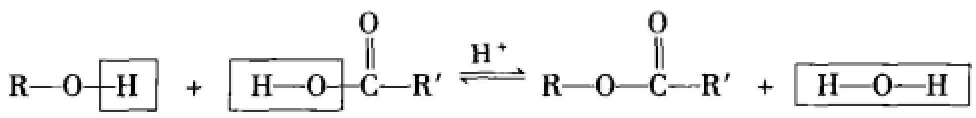
(b) 

(c) 

(d) 

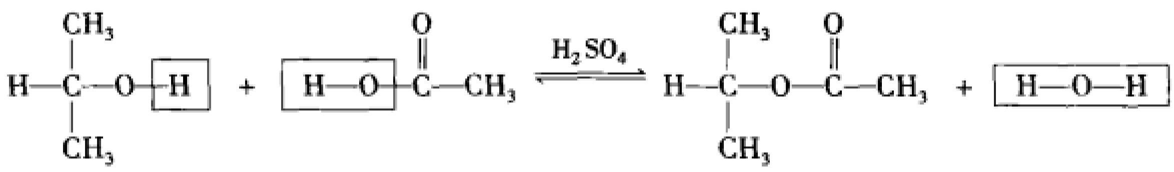
15−11 Esterification of Alcohols

To an organic chemist, the term **ester** normally means an ester of a carboxylic acid, unless some other kind of ester is specified. Replacing the —OH group of a carboxylic acid with the —OR group of an alcohol gives a carboxylic ester. The following reaction, called the **Fischer esterification**, shows the relationship between the alcohol and the acid on the left and the ester and water on the right.



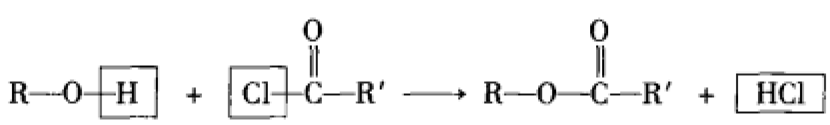
alcohol acid ester

For example, if we mix isopropyl alcohol with acetic acid and add a drop of sulfuric acid as a catalyst, the following equilibrium results.



isopropyl alcohol acetic acid isopropyl acetate water

Because the Fischer esterification is an equilibrium (often with an unfavorable equilibrium constant), clever techniques are often required to achieve good yields of esters. For example, we can use a large excess of the alcohol or the acid. Adding a dehydrating agent removes water (one of the products), driving the reaction to the right. There is a more powerful way to form an ester, however, without having to deal with an unfavorable equilibrium. An alcohol reacts with an acid chloride in an exothermic reaction to give an ester.



alcohol acid chloride ester

The mechanisms of these reactions that form acid derivatives are covered with similar mechanisms in Chapter 22.

15−12 Reactions of Alkoxides

In Section 14−5B, we learned to remove the hydroxyl proton from an alcohol by reduction with an "active" metal such as sodium or potassium. This reaction generates a sodium or potassium salt of an **alkoxide ion** and hydrogen gas.

$$R{-}\ddot{\underset{\cdot\cdot}{O}}{-}H + Na \longrightarrow R{-}\ddot{\underset{\cdot\cdot}{O}}{:}^{-}\,{}^{+}Na + 1/2H_2\uparrow$$

$$R{-}\ddot{\underset{\cdot\cdot}{O}}{-}H + K \longrightarrow R{-}\ddot{\underset{\cdot\cdot}{O}}{:}^{-}\,{}^{+}K + 1/2H_2\uparrow$$

The reactivity of alcohols toward sodium and potassium decreases in the order: methyl $> 1° > 2° > 3°$. Sodium reacts quickly with primary alcohols and some secondary alcohols. Potassium is more reactive than sodium and is commonly used with tertiary alcohols and some secondary alcohols.

Some alcohols react sluggishly with both sodium and potassium. In these cases, a useful alternative is sodium hydride, usually in tetrahydrofuran solution. Sodium hydride reacts quickly to form the alkoxide, even with

difficult compounds.

$$\underset{\text{alcohol}}{R-\ddot{O}-H} + \underset{\text{sodium hydride}}{NaH} \xrightarrow[\text{THF}]{} \underset{\text{sodium alkoxide}}{R-\ddot{O}:^- Na^+} + \underset{\text{hydrogen}}{H_2\uparrow}$$

The alkoxide ion is a strong nucleophile as well as a powerful base. Unlike the alcohol itself, the alkoxide ion reacts with primary alkyl halides and tosylates to form **ethers**. This general reaction, called the **Williamson ether synthesis**, is an S_N2 displacement. The alkyl halide (or tosylate) must be primary so that a back-side attack is not hindered. When the alkyl halide is not primary, elimination usually results.

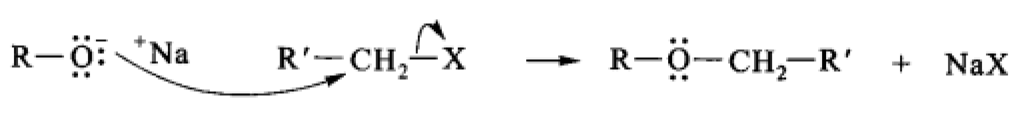
KEY MECHANISM 15-6 The williamson Ether Synthesis

This is the most important method for making ethers.

Step 1: Form the alkoxide of the alcohol having the more hindered group.

$$R-\ddot{O}-H + Na\ (\text{or NaH or K}) \longrightarrow \underset{\text{alkoxide ion}}{R-\ddot{O}:^- \quad Na^+} + 1/2H_2\uparrow$$

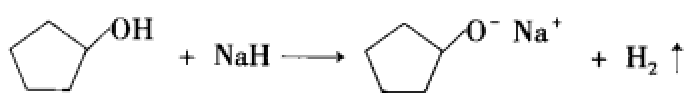
Step 2: The alkoxide displaces the leaving group of a good S_N2 substrate.



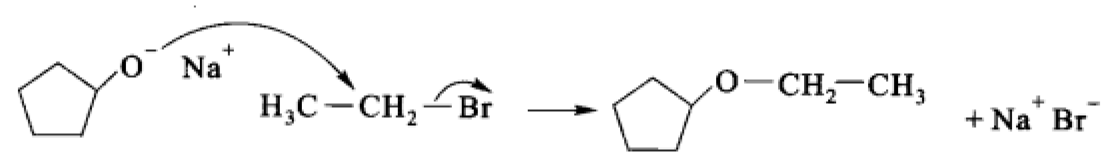
alkoxide ion primary halide or tosylate ether

Example: **Synthesis of cyclopentyl ethyl ether**

Step 1: Form the alkoxide of the alcohol with the more hindered group.



Step 2: The alkoxide displaces the leaving group of a good S_N2 substrate.



In using the Williamson ether synthesis, one must remember that the alkyl halide (or tosylate) must be a good S_N2 substrate, usually primary. In proposing a Williamson synthesis, we usually choose the less hindered alkyl group to be the halide (or tosylate) and the more hindered group to be the alkoxide ion.

PROBLEM 15-20

(a) Show how ethanol and cyclohexanol may be used to synthesize cyclohexyl ethyl ether (tosylation followed by the williamson ether synthesis).

(b) Why can't we synthesize this product simply by mixing the two alcohols, adding some sulfuric acid, and heating?

PROBLEM 15-21

A student wanted to make (*R*)-2-ethoxybutane, using the Williamson ether synthesis. He remembered that the williamson synthesis involves an S_N2 displacement, which takes place with inversion of configuration. He ordered a bottle of (*S*)-2-butanol for his chiral starting material. He also remembered that the S_N2 goes best on primary halides and tosylates, so he made ethyl tosy-

late and sodium (*S*)-2-butoxide. After warming these reagents together, he obtained an excellent yield of 2-ethoxybutane.

(a) What enantiomer of 2-ethoxybutane did he obtain? Explain how this enantiomer results from the S_N2 reaction of ethyl tosylate with sodium (*S*)-2-butoxide.

(b) What would have been the best synthesis of (*R*)-2-ethoxybutane?

(c) How can this student convert the rest of his bottle of (*S*)-2-butanol to (*R*)-2-ethoxybutane?

PROBLEM 15-22

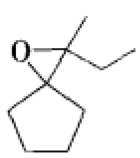
The anions of phenols (phenoxide ions) may be used in the Williamson ether synthesis, especially with very reactive alkylating reagents such as dimethyl sulfate. Using phenol, dimethyl sulfate, and other necessary reagents, show how you would synthesize methyl phenyl ether.

PROBLEM 15-23

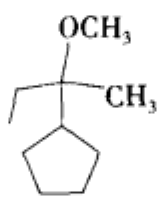
Develop syntheses for the following compounds. As starting materials, you may use cyclopentanol, alcohols containing no more than four carbon atoms, and any common reagents and solvents.

(a) *trans*-cyclopentane-1,2-diol **(b)** 1-chloro-1-ethylcyclopentane

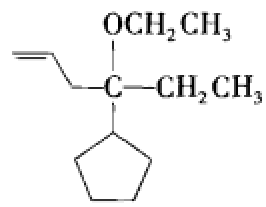
(c)



(d)



(e)



Summary in Chinese

本章概要

一、醇的酸碱性

醇羟基中的氢具有一定的酸性,可与强碱反应生成烃氧负离子,或与活泼金属(Na、K)反应,生成醇盐并放出氢气。醇的碳链上带吸电子基团使其酸性增强,而带给电子基团使其酸性减弱。酚氧离子的共振稳定化使酚的酸性明显大于醇,酚可溶于 NaOH 水溶液。醇羟基中氧原子上的孤对电子具有路易斯碱性,可作为弱的亲核试剂,与强质子酸或路易斯酸生成鎓盐。

二、醇的氧化反应(oxidation reactions of alcohols)

1. 伯醇氧化为羧酸的反应(oxidation of primary alcohols to carboxylic acids, Section 15-2B)

$$R{-}CH_2{-}OH \xrightarrow[\substack{\text{or (1) } KMnO_4,\ {}^-OH,\ H_2O,\ \Delta \\ (2)\ H_3O^+ \\ \text{or } HNO_3}]{Na_2Cr_2O_7,\ H_2SO_4} R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OH$$

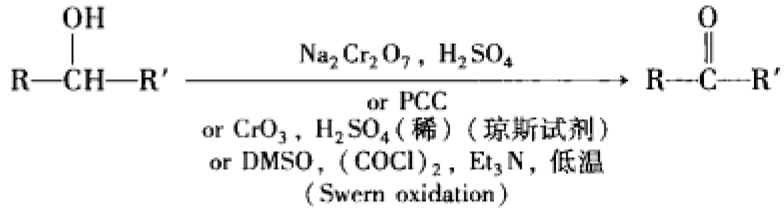
☆ 重铬酸钠与硫酸反应原位生成铬酸,铬酸氧化伯醇第一步生成的醛很容易被进一步氧化生成羧酸,此反应可高产率合成羧酸,但不适用于合成醛。用 $KMnO_4$ 作氧化剂时,反应物分子中不能有碳碳不饱和键。

2. 伯醇氧化为醛的反应(oxidation of primary alcohols to aldehydes, Section 15-2B)

$$R{-}CH_2{-}OH \xrightarrow[\substack{\text{or DMSO, } (COCl)_2,\ Et_3N,\ \text{低温} \\ \text{(Swern oxidation)}}]{PCC} R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}H$$

☆ PCC═$C_5H_5N \cdot CrO_3 \cdot HCl$，一种络合盐，又称沙瑞特（Sarrett）试剂，是一种温和的氧化剂，可选择性氧化伯醇制备醛，与 C═C、C═N 等基团不反应；Collins 试剂（$CrO_3 \cdot 2C_5H_5N$）对伯醇的氧化作用与 PCC 相同；Swern 氧化反应可在低温下将伯醇氧化成醛，醛不发生进一步的氧化反应，分子中存在的双键、三键在反应中不受影响，是实验室合成醛的有效方法。

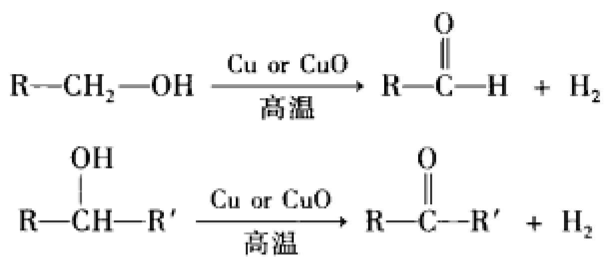
3. 仲醇氧化为酮的反应（oxidation of secondary alcohols to ketones，Section 15−2A）



☆ 这四种试剂都能将仲醇氧化为酮，但琼斯（Jones）试剂、PCC 和 DMSO/$(COCl)_2$ 氧化剂较为温和，分子中双键和三键不被氧化。

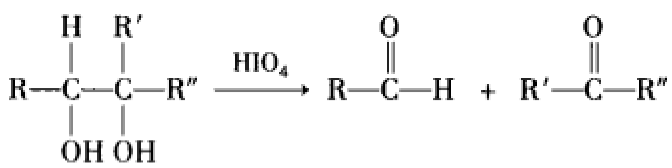
☆ 叔醇一般不被氧化。铬酸氧化伯、仲醇时溶液从橙色变为蓝绿色，因此，可以用琼斯试剂检测伯、仲醇。

4. 伯醇、仲醇催化脱氢反应（catalytic dehydrogenation of primary and secondary alcohols，Section 15−3）



☆ 此反应是工业上生产小分子醛酮的重要方法。反应是吸热的，需要 300 ℃ 以上高温，常在产物中加入适量空气与生成的氢反应放出热，又称为氧化脱氢反应。

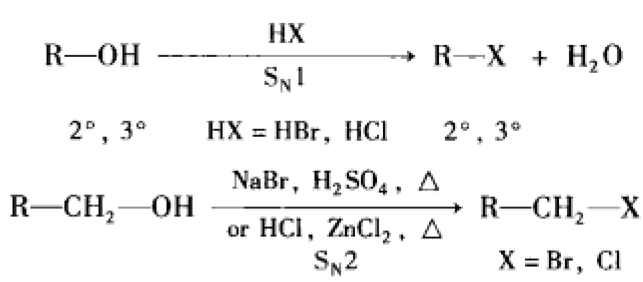
5. 邻二醇高碘酸氧化断裂反应（oxidative cleavage of glycols by periodic acid，Section 15−10B）



☆ 此反应可用于确定糖的结构。

三、醇的取代反应（substitution of alcohol hydroxyl group）

1. 醇与氢卤酸的反应（reactions of alcohols with hydrohalic acids，Section 15−6）



☆ 仲醇、叔醇与氢卤酸经过 S_N1 机理进行反应，大多数伯醇按 S_N2 机理进行反应。伯醇与氢氯酸的反应必须加入 $ZnCl_2$ 促进反应进行。$HCl/ZnCl_2$ 称为卢卡斯（Lucas）试剂，伯、仲、叔醇与卢卡斯试剂的反应速率明显不同（叔醇 > 仲醇 > 伯醇），可用卢卡斯试剂鉴别小于六个碳的伯、仲、叔醇。采用这类反应从醇制备卤代烷时应注意，由于仲醇和空阻大的伯醇反应中会发生碳正离子重排，而且生成伯、仲氯代产物的产率很低，因此，这类反应只适用于从叔醇出发制备叔卤代化合物。

2. 醇与卤化磷的反应（reactions of alcohols with phosphorus halides，Section 15−7）

$$\underset{1°,\ 2°}{R\text{—}OH} \xrightarrow[\text{or }PCl_5,\ \text{or }P,\ I_2]{PX_3} \underset{1°,\ 2°}{R\text{—}X}$$

$$PX_3 = PBr_3,\ PCl_3$$

☆ 伯醇、仲醇与卤化磷经过 S_N2 机理进行反应，反应中不发生重排，被进攻的碳原子构型转化。此反应可用于从伯醇、仲醇出发制备相应的卤代化合物，尤其是制备溴代和碘代化合物，产率较高，不适用于从叔醇出发制备叔卤代化合物。

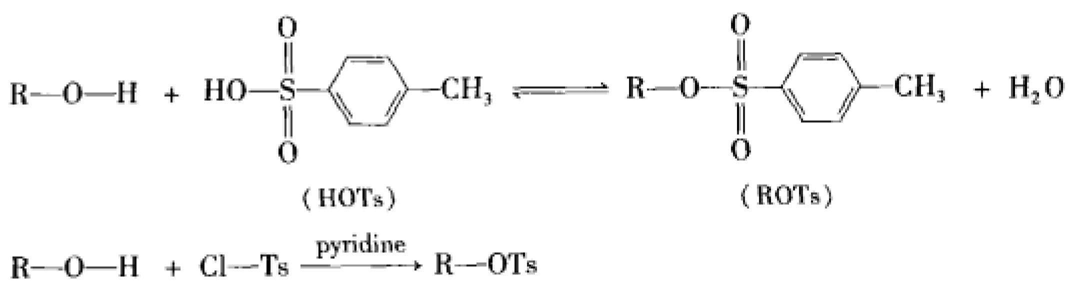
3. 醇与氯化亚砜的反应（reactions of alcohols with thionyl chloride，Section 15－8）

$$R\text{—}OH \xrightarrow{SOCl_2} R\text{—}Cl$$

☆ 醇与氯化亚砜经过分子内亲核取代机理进行反应，反应中不发生重排。由于亲核试剂从离去基团同侧进攻碳原子，因此，被进攻的碳原子构型保持。当向反应体系中加入叔胺或吡啶时，反应经过 S_N2 机理，被“游离”的氯离子亲核进攻的碳原子构型转化。这一反应是实验室以伯醇、仲醇为反应物制备氯代烃的有效方法，产率一般高于醇与三氯化磷或五氯化磷的反应。

四、醇与酸和酰氯的反应（reactions of alcohols with acids and acid chlorides）

1. 生成对甲苯磺酸酯的反应（formation of tosylate ester，Section 15－4）：



☆ 醇与磺酸的脱水酯化反应为可逆反应，必须不断除去水，以提高醇和磺酸的转化率；醇与磺酰氯的反应为不可逆反应，能够高产率地生成磺酸酯。对甲基磺酸根（^-OTs）是很好的离去基团，因此，对甲苯磺酸酯（ROTs）容易与亲核试剂（^-OH、$^-C{\equiv}N$、X^-、$^-OR'$、NH_3、$LiAlH_4$）发生 S_N2 取代反应。从伯醇和空阻小的仲醇出发，通过对甲苯磺酸酯中间体可以制备腈、醚、胺、卤代烃等多种有机化合物。为减少 E2 消除副产物，用强碱 ^-OH、$^-OR'$、$^-C{\equiv}N$ 作亲核试剂时，反应物 ROTs 中 R 应为伯烷基，当 R 为仲或叔烷基时，容易发生 E2 消除反应，生成烯烃。

2. 生成羧酸酯的反应（formation of carboxylic esters，Section 15－11）：

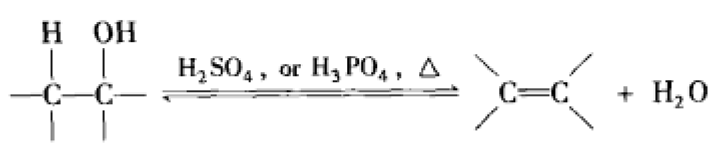
$$R\text{—}O\text{—}H + HO\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}R' \underset{\text{(Fischer 酯化反应)}}{\overset{H^+}{\rightleftharpoons}} R\text{—}O\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}R' + H_2O$$

$$R\text{—}O\text{—}H + Cl\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}R' \longrightarrow R\text{—}O\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}R' + HCl$$

☆ 醇与羧酸的反应和醇与磺酸的反应相似，为可逆反应。醇与酰氯的反应为不可逆反应，高产率生成酯。

五、醇的脱水反应（dehydration of alcohols）

1. 分子内脱水反应生成烯烃（intramolecular dehydration of alcohols to form alkenes，Section 15－9A）：



☆ 硫酸或磷酸存在下，醇分子内脱水经过 E1 机理进行反应，可能发生重排生成更稳定的碳正离子中间体。反应活性：叔醇 > 仲醇 > 伯醇，叔醇脱水用稀酸即可，而伯醇脱水需要用浓硫酸。反应符合 Zaitsev

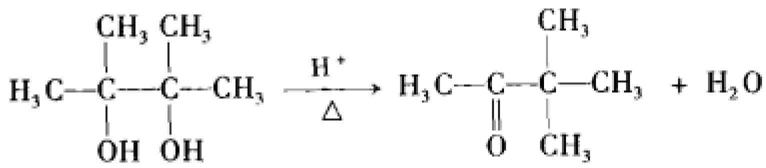
规则,双键碳原子上取代基多的烯烃为主产物。

2. 分子间脱水反应生成醚(intermolecular dehydration of alcohols to form ethers, Section 15-9B):

$$2\ R\text{—}OH \xrightleftharpoons{H^+,\ \Delta} R\text{—}O\text{—}R + H_2O$$

☆ 伯醇分子间脱水生成醚的反应经过 S_N2 机理,工业上用此方法由甲醇或小分子伯醇制备对称的二烷基醚。醇的分子内和分子间脱水反应为竞争反应,一般通过控制反应温度使反应选择性生成醚或烯烃。

3. 频哪醇脱水反应(频哪醇重排, pinacol rearrangement, Section 15-10A):



(频哪醇) (频哪酮)

☆ 其他与频哪醇相似的邻二醇亦可发生重排。在不对称的频哪醇重排时,第一步总是以生成最稳定的碳正离子为主,第二步重排反应中氢和苯基优先于甲基发生 1,2-转移。

六、醇与活泼金属和金属氢化物的反应(reactions of alcohols with an active metal and a metal hydride, Section 15-12)

$$R\text{—}OH + Na\ (\text{or } K) \longrightarrow R\text{—}O^{-}\,{}^{+}Na + 1/2\ H_2\uparrow$$

$$R\text{—}OH + NaH \longrightarrow R\text{—}O^{-}\,{}^{+}Na + H_2\uparrow$$

☆ 反应生成的烷氧基钠或钾为强碱,可原位用于 Williamson 醚合反应。

Essential Problem-Solving Skills in Chapter 15

1. Identify whether oxidation or reduction is needed to interconvert alkanes, alcohols, aldehydes, ketones, and acids, and identify reagents that will accomplish the conversion.
2. Predict the products of the reactions of alcohols with
   (**a**) Oxidizing and reducing agents.
   (**b**) Carboxylic acids and acid chlorides.
   (**c**) Dehydrating reagents, especially H_2SO_4 and H_3PO_4.
   (**d**) Inorganic acids.
   (**e**) Sodium, potassium, and sodium hydride.
3. Predict the products of reactions of alkoxide ions.
4. Propose chemical tests to distinguish alcohols from the other types of compounds we have studied.
5. Use your knowledge of alcohol and diol reactions to propose mechanisms and products of similar reactions you have never seen before.
6. Show how to convert an alcohol to a related compound with a different functional group.
7. Predict the products of pinacol rearrangement and periodate cleavage of glycols.
8. Use retrosynthetic analysis to propose effective single-step and multistep syntheses of compounds using alcohols as intermediates (especially those using Grignard and organolithium reagents to assemble the carbon skeletons).

Study Problems

15-24 Briefly define each term, and give an example.

(a) oxidation
(b) reduction
(c) chromic acid oxidation
(d) PCC oxidation
(e) ether
(f) Williamson ether synthesis
(g) alkoxide ion
(h) carboxylic ester
(i) Fischer esterification
(j) tosylate ester（对甲基磺酸酯）
(k) Lucas test
(l) pinacol rearrangement

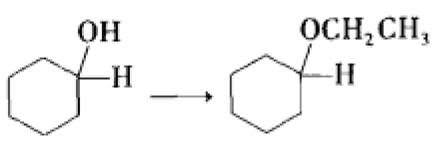
15−25 In each case, show how you would synthesize the chloride, bromide, and iodide from the corresponding alcohol.

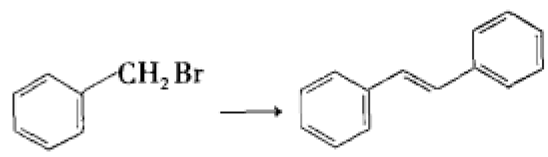
(a) 1-halobutane (halo = chloro, bromo, iodo)
(b) halocyclopentane
(c) 1-halo-1-methylcyclohexane
(d) 1-halo-2-methylcyclohexane

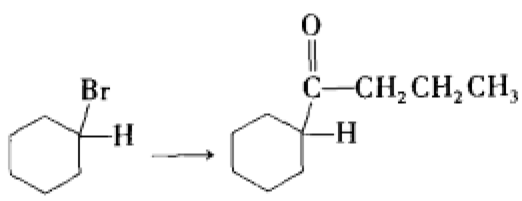
15−26 Predict the major products of the following reactions, including stereochemistry where appropriate.

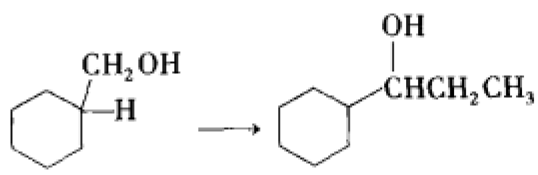
(a) (*R*)-2-butanol + TsCl in pyridine
(b) (*S*)-2-butyl tosylate + NaBr
(c) cyclooctanol + CrO_3/H_2SO_4
(d) cyclopentylmethanol + $CrO_3\cdot$pyridine$\cdot$HCl
(e) cyclopentylmethanol + $Na_2Cr_2O_7/H_2SO_4$
(f) cyclopentanol + $HCl/ZnCl_2$
(g) *n*-butanol + HBr
(h) cyclooctylmethanol + CH_3CH_2MgBr
(i) potassium *t*-butoxide + methyl iodide
(j) sodium methoxide + *t*-butyl iodide
(k) cyclopentanol + H_2SO_4/heat
(l) product from (k) + OsO_4/H_2O_2, then HIO_4
(m) sodium ethoxide + 1-bromobutane
(n) sodium ethoxide + 2-methyl-2-bromobutane

15−27 Show how you would accomplish the following synthetic conversions.

(a) 

(b) 2 

(c) 

(d) 

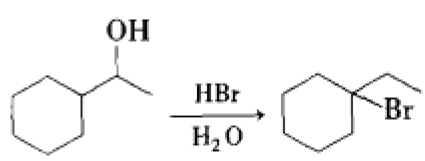
15−28 Predict the major products of dehydration catalyzed by sulfuric acid.

(a) 1-hexanol
(b) 2-hexanol
(c) 3-pentanol
(d) 1-methylcyclopentanol
(e) cyclopentylmethanol
(f) 2-methylcyclopentanol

15−29 Show how you would convert (*S*)-2-hexanol to

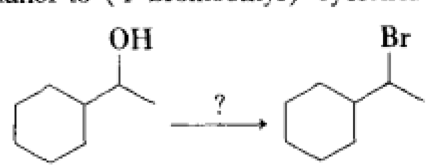
(a) (*S*)-2-chlorohexane
(b) (*R*)-2-bromohexane
(c) (*R*)-2-hexanol

15−30 When 1-cyclohexylethanol is treated with concentrated aqueous HBr, the major product is 1-bromo-1-ethylcyclohexane.

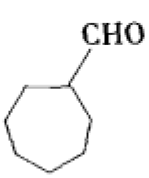


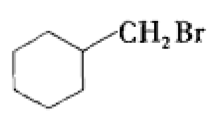
(a) Give a mechanism for this reaction.

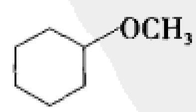
(b) How would you convert 1-cyclohexylethanol to (1-bromoethyl) cyclohexane in good yield?

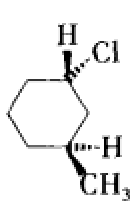


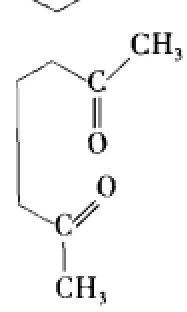
15−31 Show how you would make each compound, beginning with an alcohol of your choice.

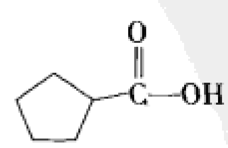
(a) 

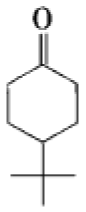
(b) 

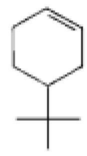
(c) 

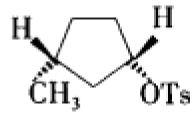
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

(j)

15−32 Predict the major products (including stereochemistry) when *cis*-3-methylcyclohexanol reacts with the following reagents.

(a) PBr_3 (b) $SOCl_2$ (c) Lucas reagent
(d) concentrated HBr (e) TsCl/pyridine, then NaBr

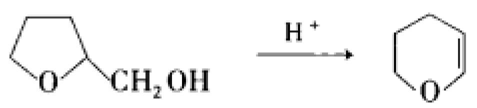
15−33 Show how you would use simple chemical tests to distinguish between the following pairs of compounds. In each case, describe what you would do and what you would observe.

(a) 1-butanol and 2-butanol (b) 2-butanol and 2-methyl-2-butanol
(c) cyclohexanol and cyclohexene (d) cyclohexanol and cyclohexanone
(e) cyclohexanone and 1-methylcyclohexanol

15−34 Compound **A** is an optically active alcohol. Treatment with chromic acid converts **A** into a ketone, **B**. In a separate reaction, **A** is treated with PBr_3, converting **A** into compound **C**. Compound **C** is purified, and then it is allowed to react with magnesium in ether to give a Grignard reagent, **D**. Compound **B** is added to the resulting solution of the Grignard reagent. After hydrolysis of the initial product (**E**), this solution is found to contain 3,4-dimethyl-3-hexanol. Propose structures for compounds **A**, **B**, **C**, **D**, and **E**.

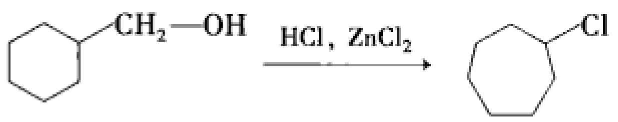
$$\mathbf{A} \xrightarrow{PBr_3} \mathbf{C} \xrightarrow{\text{Mg, ether}} \mathbf{D}\ (\text{Grignard reagent})$$
$$\mathbf{A} \xrightarrow{Na_2Cr_2O_7,\ H_2SO_4} \mathbf{B}$$
$$\mathbf{D} + \mathbf{B} \longrightarrow \mathbf{E} \xrightarrow{H_3O^+} \text{3,4-dimethyl-3-hexanol}$$

15−35 Under acid catalysis, tetrahydrofurfuryl alcohol reacts to give surprisingly good yields of dihydropyran. Propose a mechanism to explain this useful synthesis.

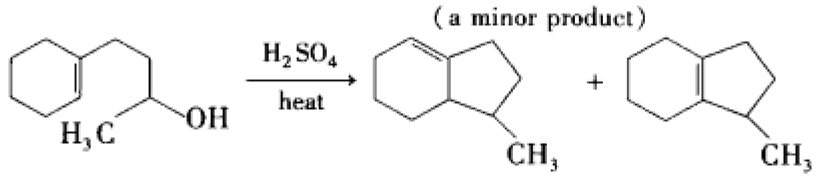


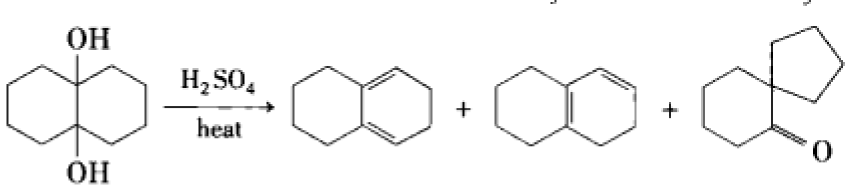
tetrahydrofurfuryl alcohol dihydropyran

15−36 Propose mechanisms for the following reactions. In most cases, more products are formed than are shown here. You only need to explain the formation of the products shown, however.

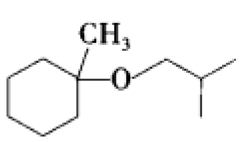
(a) 

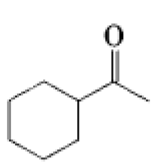
(a minor product)

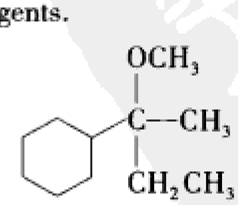
(b) 

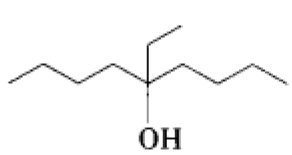
(c) 

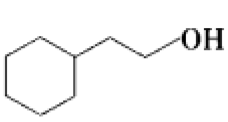
15−37 Show how you would synthesize the following compounds. As starting materials, you may use any alcohols containing four or fewer carbon atoms, cyclohexanol, and any necessary solvents and inorganic reagents.

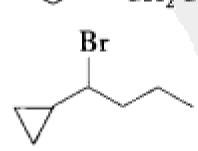
(a) 

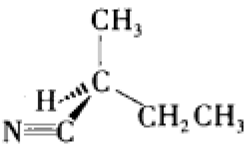
(b) 

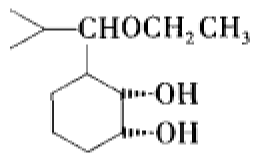
(c) 

(d) 

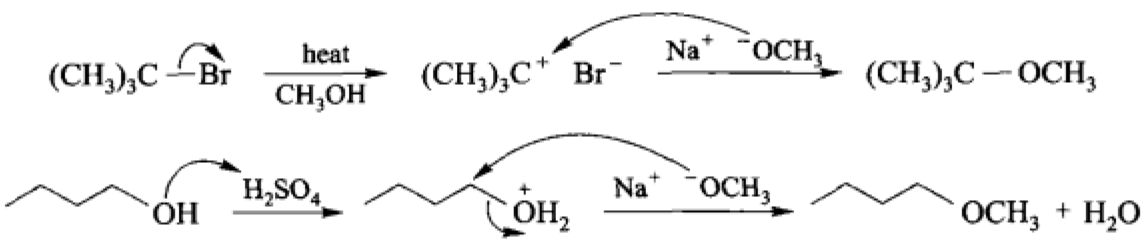
(e) 

(f) 

(g) 

*(h) 

15−38 The following pseudo-syntheses (guaranteed not to work) exemplify a common conceptual error.



(**a**) What is the conceptual error implicit in these syntheses?

(**b**) Propose syntheses that are more likely to succeed.

15−39 Two unknowns, **X** and **Y**, both having the molecular formula C_4H_8O, give the following results with four chemical tests. Propose structures for **X** and **Y** consistent with this information.

	Bromine	Na Metal	Chromic Acid	Lucas Reagent
Compound **X**	decolorizes	bubbles	orange to green	no reaction
Compound **Y**	no reaction	no reaction	no reaction	no reaction

Chapter 16

Ethers, Epoxides, and Sulfides

16−1 Introduction

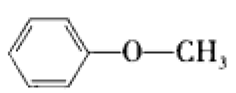
Ethers are compounds of formula R—O—R′, where R and R′ may be alkyl groups or aryl (benzene ring) groups. Like alcohols, ethers are related to water, with alkyl groups replacing the hydrogen atoms. In an alcohol, one hydrogen atom of water is replaced by an alkyl group. In an ether, both hydrogens are replaced by alkyl groups. The two alkyl groups are the same in a **symmetrical ether** and different in an **unsymmetrical ether**.

H—O—H	R—O—H	R—O—R′
water	alcohol	ether

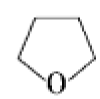
Examples of ethers

$CH_3CH_2—O—CH_2CH_3$

diethyl ether
(乙醚)
(a symmetrical ether)



methyl phenyl ether
(甲基苯基醚,茴香醚)
(an unsymmetrical ether)



tetrahydrofuran
(四氢呋喃)
(a symmetrical, cyclic ether)

As with other functional groups, we will discuss how ethers are formed and how they react. Ethers (other than epoxides) are relatively unreactive, however, and they are not frequently used as synthetic intermediates. Because they are stable with many types of reagents, ethers are commonly used as solvents for organic reactions. In this chapter, we consider the properties of ethers and how these properties make ethers such valuable solvents for organic reactions.

The most important commercial ether is diethyl ether, often called "ethyl ether," or simply "ether." Ether is a good solvent for reactions and extractions, and it is used as a volatile starting fluid for diesel and gasoline engines. Ether was used as a surgical anesthetic for over a hundred years (starting in 1842), but it is highly flammable, and patients often vomited as they regained consciousness. Several compounds that are less flammable and more easily tolerated are now in use, including nitrous oxide (N_2O) and halothane ($CF_3—CHClBr$).

16−2 Physical Properties of Ethers

16−2A Structure and Polarity of Ethers

Like water, ethers have a bent structure, with an sp^3 hybrid oxygen atom giving a nearly tetrahedral bond angle.

In water, the nonbonding electrons compress the H—O—H bond angle to 104.5°, but in a typical ether, the bulk of the alkyl groups enlarges the bond angle. Figure 16−1 shows the structure of dimethyl ether, with a tetrahedral bond angle of 110°.

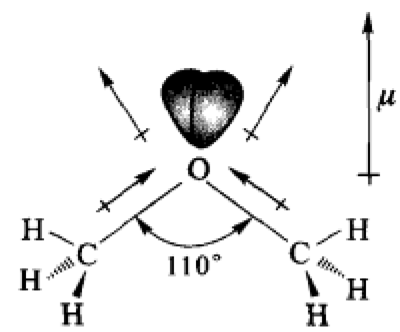
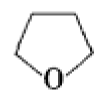


Figure 16−1 Structure of dimethyl ether.

Although ethers lack the polar hydroxyl group of alcohols, they are still strongly polar compounds. The dipole moment of an ether is the vector sum of two polar C—O bonds, with a substantial contribution from the two lone pairs of electrons. Table 16−1 compares the dipole moments of dimethyl ether, diethyl ether, and tetrahydrofuran (THF) with those of alkanes and alcohols of similar molecular weights. An ether such as THF provides a strongly polar solvent without the reactivity of a hydroxyl group.

TABLE 16−1 Comparison of the Boiling Points of Ethers, Alkanes, and Alcohols of Similar Molecular Weights

Compound	Formula	MW	bp/℃	Dipole Moment(D)
water	H_2O	18	100	1.9
ethanol	$CH_3CH_2—OH$	46	78	1.7
dimethyl ether	$CH_3—O—CH_3$	46	−25	1.3
propane	$CH_3CH_2CH_3$	44	−42	0.1
n-butanol	$CH_3CH_2CH_2CH_2—OH$	74	118	1.7
tetrahydrofuran (四氢呋喃)		72	66	1.6
diethyl ether	$CH_3CH_2—O—CH_2CH_3$	74	35	1.2
pentane	$CH_3CH_2CH_2CH_2CH_3$	72	36	0.1

Note: The alcohols are hydrogen bonded, giving them much higher boiling points. The ethers have boiling points that are closer to those of alkanes with similar molecular weights.

16−2B Boiling Points of Ethers; Hydrogen Bonding

Table 16−1 compares the boiling points of several ethers, alcohols, and alkanes. Notice that the boiling points of dimethyl ether and diethyl ether are nearly 100 ℃ lower than those of alcohols having similar molecular weights. This large difference results mostly from hydrogen bonding in the alcohols. Pure ethers cannot engage in hydrogen bonding because they have no O—H groups. Ethers do have large dipole moments, resulting in dipole-dipole attractions, but these attractions appear to have relatively little effect on their boiling points.

Although pure ethers have no hydroxyl groups to engage in hydrogen bonding, they can hydrogen bond with other compounds that do have O—H or N—H groups. Figure 16−2 shows that a hydrogen bond requires both a hydrogen bond *donor* and a hydrogen bond *acceptor*. The donor is the molecule with an O—H or N—H group.

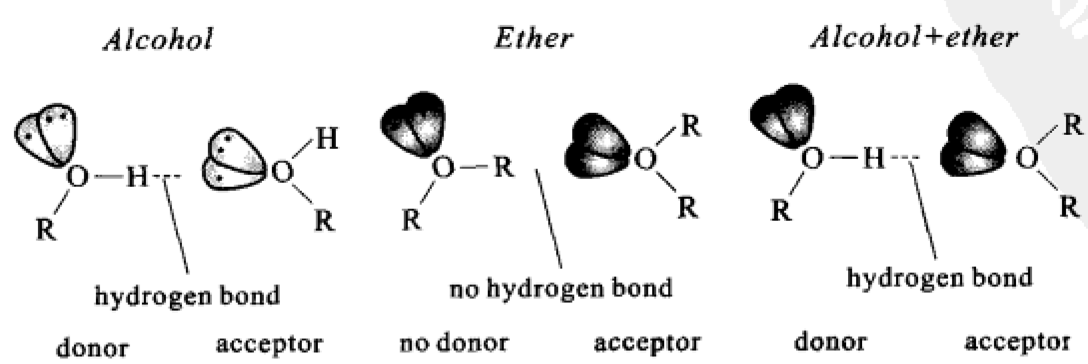
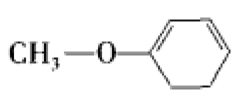
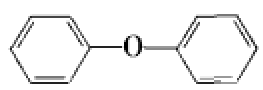
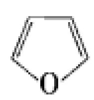
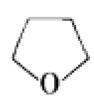
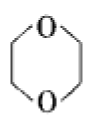


Figure 16−2 Hydrogen bonding in alcohols and ethers.

The acceptor is the molecule whose lone pair of electrons forms a weak partial bond to the hydrogen atom provided by the donor. An ether molecule has the lone pair to form a hydrogen bond with an alcohol (or other hydrogen bond donor), but it cannot form a hydrogen bond with another ether molecule. Because ether molecules are not held together by hydrogen bonds, they are more volatile than alcohols having similar molecular weights. Table 16-2 lists the physical properties of a representative group of common ethers.

TABLE 16-2 Physical Properties of Some Representative Ethers

Name	Structure	mp/℃	bp/℃	Density/($g\cdot mL^{-1}$)
dimethyl ether	$CH_3—O—CH_3$	-140	-25	0.66
ethyl methyl ether	$CH_3CH_2—O—CH_3$		8	0.72
diethyl ether	$CH_3CH_2—O—CH_2CH_3$	-116	35	0.71
di-*n*-propyl ether	$CH_3CH_2CH_2—O—CH_2CH_2CH_3$	-122	91	0.74
diisopropyl ether	$(CH_3)_2CH—O—CH(CH_3)_2$	-86	68	0.74
1,2-dimethoxyethane (DME) (1,2-二甲氧基乙烷,乙二醇二甲醚)	$CH_3—O—CH_2CH_2—O—CH_3$	-58	83	0.86
methyl phenyl ether (anisole)		-37	154	0.99
diphenyl ether		27	259	1.07
furan(呋喃)		-86	32	0.94
tetrahydrofuran (THF) (四氢呋喃)		-108	65	0.89
1,4-dioxane (1,4-二氧杂环己烷,1,4-二噁烷,1,4-二氧六环)		11	101	1.03

16-2C Ethers as Polar Solvents

Ethers are ideally suited as solvents for many organic reactions. They dissolve a wide range of polar and nonpolar substances, and their relatively low boiling points simplify their evaporation from the reaction products. Nonpolar substances tend to be more soluble in ethers than in alcohols because ethers have no hydrogen-bonding network to be broken up by the nonpolar solute.

Polar substances tend to be nearly as soluble in ethers as in alcohols because ethers have large dipole moments as well as the ability to serve as hydrogen bond acceptors. The nonbonding electron pairs of an ether effectively solvate cations, as shown in Figure 16-3. Ethers do not solvate anions as well as alcohols do, however.

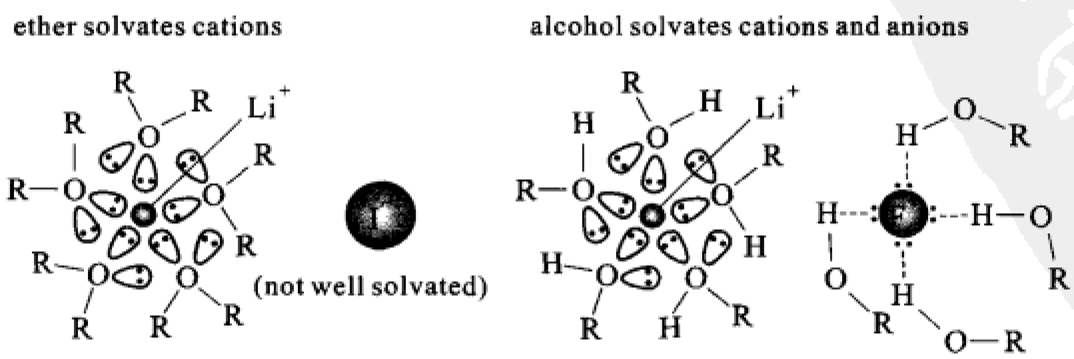


Figure 16-3 Ethers solvate cations

Ionic substances with small, "hard" anions requiring strong solvation to overcome their ionic bonding are often insoluble in ether solvents. Substances with large, diffuse anions, such as iodides, acetates, and other organic anions, tend to be more soluble in ether solvents than substances with smaller, harder anions.

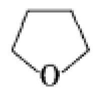
Alcohols cannot be used as solvents for reagents that are more strongly basic than the alkoxide ion. The hydroxyl group quickly protonates the base, destroying the basic reagent.

$$\underset{\text{strong base}}{B:^-} + \underset{\text{alcohol}}{R{-}\ddot{O}H} \rightleftharpoons \underset{\text{protonated base}}{B{-}H} + \underset{\text{alkoxide ion}}{R{-}\ddot{O}:^-}$$

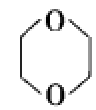
Ethers are nonhydroxylic (no hydroxyl group), and they are normally unreactive toward strong bases. For this reason, ethers are frequently used as solvents for very strong polar bases (like the Grignard reagent) that require polar solvents. The four ethers shown here are common solvents for organic reactions. DME, THF, and dioxane are miscible with water, and diethyl ether is sparingly soluble in water.

$CH_3CH_2{-}O{-}CH_2CH_3$
diethyl ether
"ether"
bp 35 ℃

$CH_3{-}O{-}CH_2CH_2{-}O{-}CH_3$
1,2-dimethoxyethane
DME, "glyme"
bp 82 ℃



tetrahydrofuran
THF, oxolane
bp 65 ℃



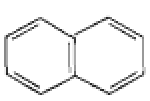
1,4-dioxane
dioxane
bp 101 ℃
(二噁烷)

PROBLEM 16-1

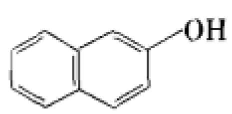
Rank the given solvents in decreasing order of their ability to dissolve each compound.

Solutes

(a) NaOAc

(b) 

naphthalene(萘)

(c) 

2-naphthol(2-萘酚)

Solvents
ethyl ether
water
ethanol
dichloromethane

16-2D Stable Complexes of Ethers with Reagents

The special properties of ethers (polarity, lone pairs, but relatively unreactive) enhance the formation and use of many reagents. For example, Grignard reagents cannot form unless an ether is present, possibly to share its lone pairs of electrons with the magnesium atom. This sharing of electrons stabilizes the reagent and helps keep it in solution (Figure 16-4).

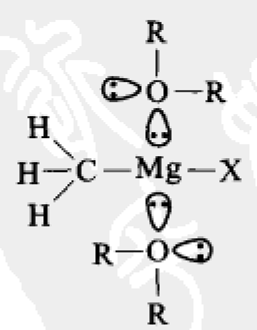
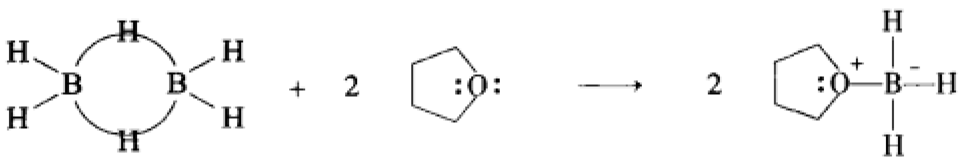


Figure 16-4 Complexation of an ether with a Grignard reagent stabilizes the reagent and helps keep it in solution.

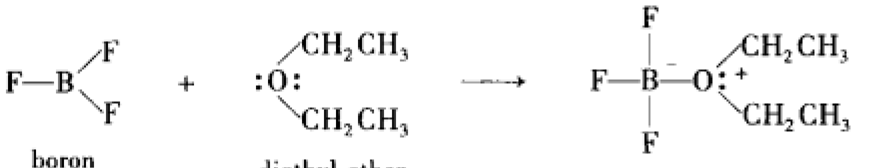
Complexes with Electrophiles An ether's nonbonding electrons also stabilize borane, BH_3. Pure borane exists as a dimer called diborane, B_2H_6. Diborane is a toxic, flammable, and explosive gas, whose use is both dangerous and inconvenient. Borane forms a stable complex with tetrahydrofuran. The $BH_3 \cdot THF$ complex is commercially available as a 1 mol/L solution, easily measured and transferred like any other air-sensitive liquid reagent. The availability of $BH_3 \cdot$

THF has contributed greatly to the convenience of hydroboration.



diborane(乙硼烷)　　tetrahydrofuran　　$BH_3 \cdot THF$

Boron trifluoride is used as a Lewis acid catalyst in a wide variety of reactions. Like diborane, BF_3 is a toxic gas, but BF_3 forms a stable complex with ethers, allowing it to be conveniently stored and measured. The complex of BF_3 with diethyl ether is called "boron trifluoride etherate."

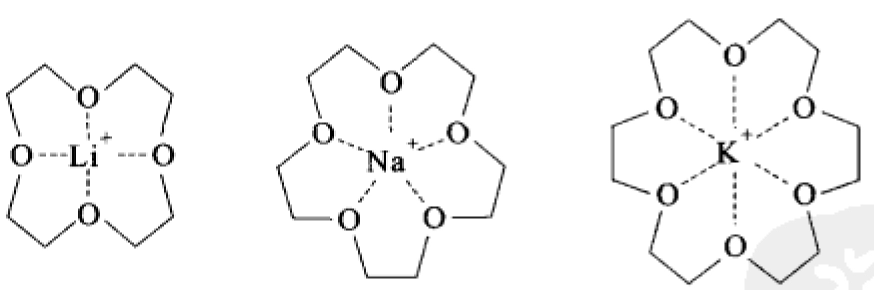


boron trifluoride　　diethyl ether　　$BF_3 \cdot OEt_2$ "boron trifluoride etherate" (三氟化硼乙醚络合物)

PROBLEM 16-2

Aluminum trichloride ($AlCl_3$) dissolves in ether with the evolution of a large amount of heat. (In fact, this reaction can become rather violent if it gets too warm.) Show the structure of the resulting aluminum chloride etherate complex.

Crown Ether Complexes In Chapter 7, we encountered the use of **crown ethers**, large cyclic polyethers that specifically solvate metal cations by complexing the metal in the center of the ring. Different crown ethers solvate different cations, depending on the relative sizes of the crown ether and the cation and the number of binding sites around the cation.



12-crown-4 solvates Li^+　　15-crown-5 solvates Na^+　　18-crown-6 solvates K^+

Complexation by crown ethers often allows polar inorganic salts to dissolve in nonpolar organic solvents. This enhanced solubility allows polar salts to be used under aprotic conditions, where the uncomplexed anions may have greatly enhanced reactivity. For example, we used 18-crown-6 to dissolve potassium fluoride in acetonitrile (CH_3CN), where the poorly solvated fluoride ion is a moderately strong nucleophile. Many other salts, including carboxylate salts ($RCOO^- \, ^+K$), cyanides (KCN), and permanganates ($KMnO_4$), can be dissolved in aprotic (and often nonpolar) organic solvents using crown ethers. In each case, the crown ether complexes only the cation, leaving the anion bare and highly reactive.

PROBLEM 16-3

In the presence of 18-crown-6, potassium permanganate dissolves in benzene to give "purple benzene," a useful reagent for oxidizing alkenes in an aprotic environment. Use a drawing of the complex to show why $KMnO_4$ dissolves in benzene and why the reactivity of the permanganate ion is enhanced.

16-3 Spectroscopy of Ethers

Infrared Spectroscopy of Ethers Infrared spectra do not show obvious or reliable absorptions for ethers. Most ethers give a moderate to strong C—O stretch around 1 000 to 1 200 cm^{-1} (in the fingerprint region), but many compounds other than ethers give similar absorptions. Nevertheless, the IR spectrum can be useful because it shows the *absence* of carbonyl (C═O) groups and hydroxyl (O—H) groups. If the molecular formula contains an oxygen atom, the lack of carbonyl or hydroxyl absorptions in the IR suggests an ether.

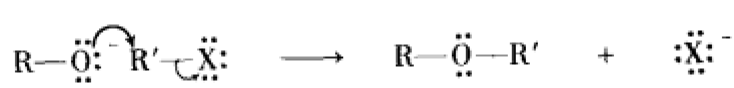
NMR Spectroscopy of Ethers In the ^{13}C NMR spectrum, a carbon atom bonded to oxygen generally absorbs between $\delta 65$ and $\delta 90$. Protons on carbon atoms bonded to oxygen usually absorb at chemical shifts between $\delta 3.5$ and $\delta 4$ in the ^1H NMR spectrum. Both alcohols and ethers have resonances in this range.

16-4 Synthesis of Ethers

We have already seen most of the common methods for synthesizing ethers. We review them at this time, looking more closely at the mechanisms to see which methods are most suitable for preparing various kinds of ethers.

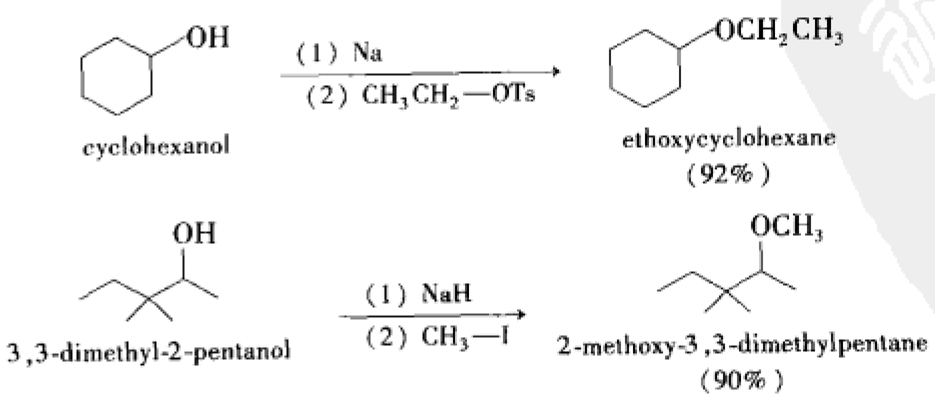
16-4A The Williamson Ether Synthesis

The **Williamson ether synthesis** is the most reliable and versatile ether synthesis. This method involves the S_N2 attack of an alkoxide ion on an unhindered primary alkyl halide or tosylate. Secondary alkyl halides and tosylates are occasionally used in the Williamson synthesis, but elimination competes, and the yields are often poor.



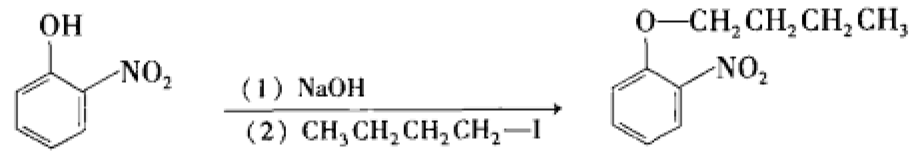
The alkoxide is commonly made by adding Na, K, or NaH to the alcohol.

Examples



Synthesis of Phenyl Ethers A phenol (aromatic alcohol) can be used as the alkoxide fragment (but not the halide fragment) for the Williamson ether synthesis. Phenols are more acidic than aliphatic alcohols, and sodium

hydroxide is sufficiently basic to form the phenoxide ion. As with other alkoxides, the electrophile should have an unhindered primary alkyl group and a good leaving group.



2-nitrophenol 2-butoxynitrobenzene (80%)

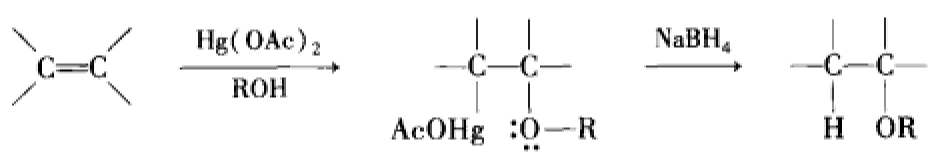
PROBLEM 16-4

Show how you would use the Williamson ether synthesis to prepare the following ethers. You may use any alcohols or phenols as your organic starting materials.

(**a**) cyclohexyl propyl ether (**b**) isopropyl methyl ether
(**c**) 1-methoxy-4-nitrobenzene (**d**) ethyl *n*-propyl ether (two ways)
(**e**) benzyl *t*-butyl ether (benzyl = Ph—CH_2—)

16-4B Synthesis of Ethers by Alkoxymercuration Demercuration

The **alkoxymercuration-demercuration** process adds a molecule of an alcohol across the double bond of an alkene. The product is an ether, as shown here.



mercurial ether

Example

$$CH_3(CH_2)_3—CH{=}CH_2 \xrightarrow[(2)\ NaBH_4]{(1)\ Hg(OAc)_2,\ CH_3OH} CH_3(CH_2)_3—\underset{\displaystyle OCH_3}{CH}—CH_3$$

1-hexene 2-methoxyhexane, 80% (Markovnikov product)

16-4C Industrial Synthesis: Bimolecular Dehydration of Alcohols

The least expensive method for synthesizing simple symmetrical ethers is the acid-catalyzed bimolecular dehydration. Unimolecular dehydration (to give an alkene) competes with bimolecular dehydration. To form an ether, the alcohol must have an unhindered primary alkyl group, and the temperature must be kept low. If the alcohol is hindered or the temperature is too high, the delicate balance between substitution and elimination shifts in favor of elimination, and very little ether is formed. Bimolecular dehydration is used in industry to make symmetrical ethers from primary alcohols. Because the dehydration is so limited in its scope, it finds little use in the laboratory synthesis of ethers.

Bimolecular dehydration

$$2R—OH \underset{}{\overset{H^+}{\rightleftharpoons}} R—O—R + H_2O$$

Examples

$$2CH_3CH_2CH_2OH \xrightarrow{H_2SO_4,\ 140\ ^\circ C} CH_3CH_2CH_2{-}O{-}CH_2CH_2CH_3 + H_2O$$

n-propyl alcohol → *n*-propyl ether (75%)

$$CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \xrightarrow{H_2SO_4,\ 140\ ^\circ C} H_2C{=}CH{-}CH_3 + H_2O$$

isopropyl alcohol → unimolecular dehydration (no ether is formed)

If the conditions are carefully controlled, bimolecular dehydration is a cheap synthesis of diethyl ether. In fact, this is the industrial method used to produce millions of gallons of diethyl ether each year.

PROBLEM 16-5

Explain why bimolecular dehydration is a poor method for making unsymmetrical ethers such as ethyl methyl ether.

PROBLEM 16-6

Propose a mechanism for the acid-catalyzed dehydration of *n*-propyl alcohol to *n*-propyl ether, as shown above. When the temperature is allowed to rise too high, propene is formed. Propose a mechanism for the formation of propene, and explain why it is favored at higher temperatures.

PROBLEM 16-7

Which of the following ethers can be formed in good yield by dehydrating the corresponding alcohols? For those that cannot be formed by dehydration, suggest an alternative method that will work.

(**a**) dibutyl ether (**b**) ethyl *n*-propyl ether (**c**) di-*sec*-butyl ether

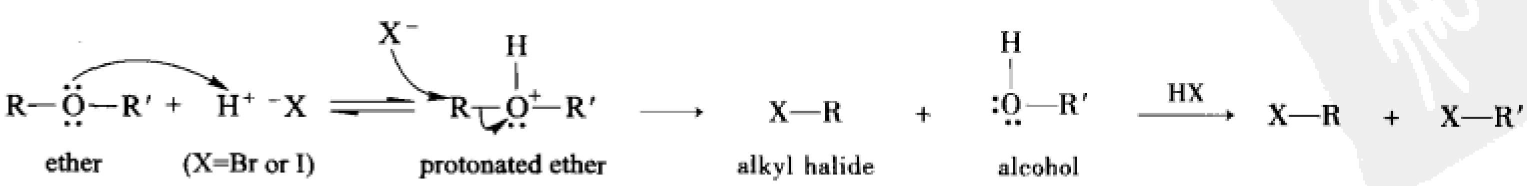
16-5 Cleavage of Ethers by HBr and HI

Unlike alcohols, ethers are not commonly used as synthetic intermediates because they do not undergo many reactions. This unreactivity makes ethers attractive as solvents. Even so, ethers do undergo a limited number of characteristic reactions.

Ethers are cleaved by heating with HBr or HI to give alkyl bromides or alkyl iodides.

$$R{-}O{-}R' \xrightarrow[(X = Br\ or\ I)]{excess\ HX} R{-}X + R'{-}X$$

Ethers are unreactive toward most bases, but they can react under acidic conditions. A protonated ether can undergo substitution or elimination with the expulsion of an alcohol. Ethers react with concentrated HBr and HI because these reagents are sufficiently acidic to protonate the ether, while bromide and iodide are good nucleophiles for the substitution.



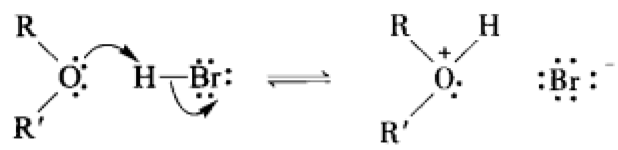
In effect, this reaction converts a dialkyl ether into two alkyl halides. The conditions are very strong, however, and the molecule must not contain any acid-sensitive functional groups.

Iodide and bromide ions are good nucleophiles but weak bases, so they are more likely to substitute by the S_N2 mechanism than to eliminate by the E2 mechanism. Mechanism 16-1 shows how bromide ion cleaves the protonated ether by displacing an alcohol. In most cases, the alcohol reacts further with HBr to give the alkyl bromide. The reaction of cyclohexyl ethyl ether with HBr is an example of this displacement. The cyclohexanol produced by the cleavage reacts further with HBr, and the final products are ethyl bromide and bromocyclohexane.

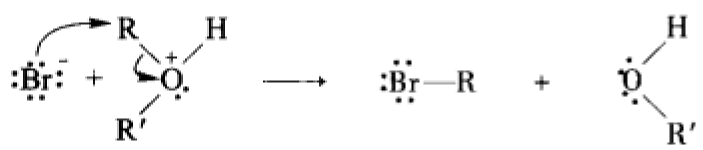
MECHANISM 16-1 Cleavage of an Ether by HBr or HI

Ethers are cleaved by a nucleophilic substitution of Br^- or I^- on the protonated ether.

Step 1: Protonation of the ether to form a good leaving group.



Step 2: S_N2 cleavage of the protonated ether.



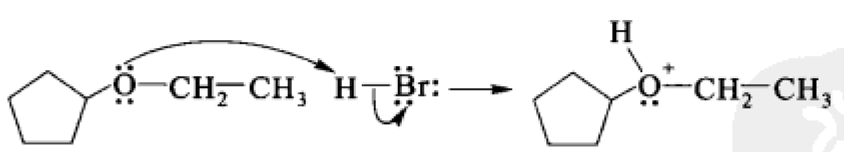
Step 3: Conversion of the alcohol fragment to the alkyl halide.
(Does not occur with phenols.)

$$R'\text{—O—H} \xrightarrow{HBr} R'\text{—Br} + H_2O$$

This conversion can occur by either of the two mechanisms shown in Section 15-6 depending on the structure of the alcohol and the reaction conditions. The protonated alcohol undergoes either S_N1 or S_N2 substitution by bromide ion.

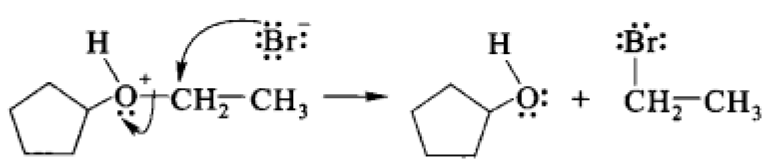
EXAMPLE: Cleavage of cyclopentyl ethyl ether by HBr.

Step 1: Protonation of the ether to form a good leaving group,

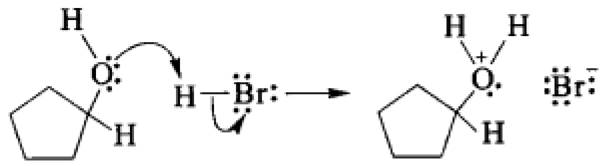


cyclopentyl ethyl ether

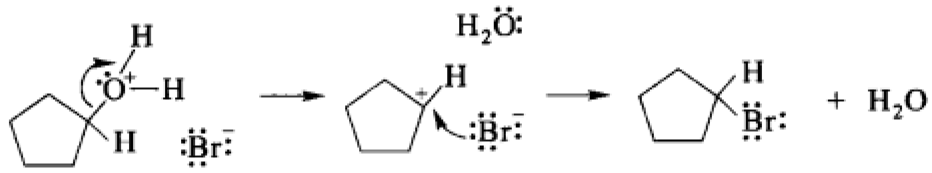
Step 2: Cleavage of the protonated ether



Step 3: Conversion of the alcohol fragment to the alkyl halide.
The alcohol is protonated to form a good leaving group.



The protonated ether undergoes S_N1 or S_N2 substitution by bromide ion.

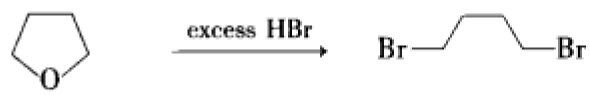


Hydroiodic acid (HI) reacts with ethers the same way HBr does. Aqueous iodide is a stronger nucleophile than aqueous bromide, and iodide reacts at a faster rate. We can rank the hydrohalic acids in order of their reactivity toward the cleavage of ethers:

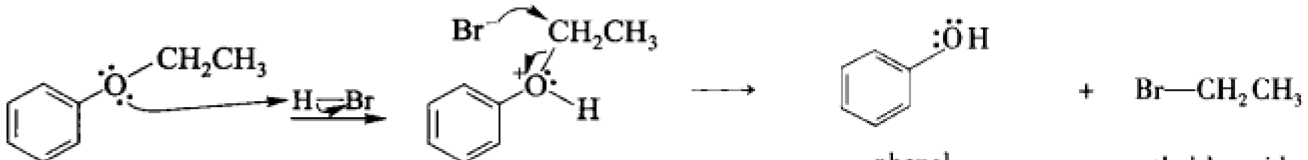
$$HI > HBr \gg HCl$$

PROBLEM 16-8

Propose a mechanism for the following reaction.



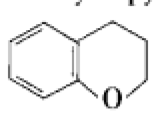
Phenyl Ethers Phenyl ethers (one of the groups bonded to oxygen is a benzene ring) react with HBr or HI to give alkyl halides and phenols. Phenols do not react further to give halides because the sp^2-hybridized carbon atom of the phenol cannot undergo the S_N2 (or S_N1) reaction needed for conversion to the halide.



PROBLEM 16-9

Predict the products of the following reactions. An excess of acid is available in each case.

(a) ethoxycyclohexane + HBr (b) tetrahydropyran + HI

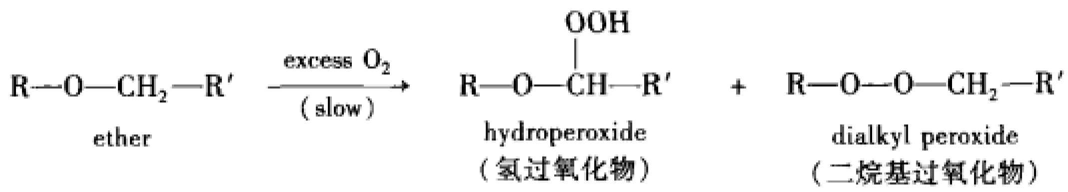
(c) anisole (methoxybenzene) + HBr (d)  + HI

(e) $Ph—O—CH_2CH_2—CH(CH_3)—CH_2—O—CH_2CH_3$ + HBr

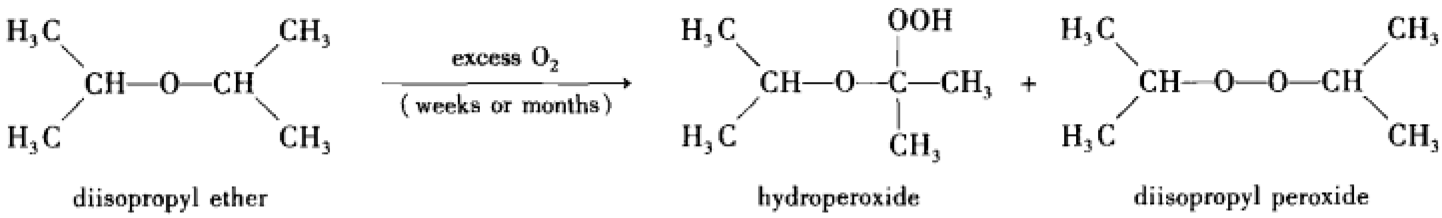
16-6 Autoxidation of Ethers

When ethers are stored in the presence of atmospheric oxygen, they slowly oxidize to produce hydroperoxides and

dialkyl peroxides, both of which are explosive. Such a spontaneous oxidation by atmospheric oxygen is called an **autoxidation**.



Example



Organic chemists often buy large containers of ethers and use small quantities over several months. Once a container has been opened, it contains atmospheric oxygen, and the autoxidation process begins. After several months, a large amount of peroxide may be present. Distillation or evaporation concentrates the peroxides, and an explosion may occur.

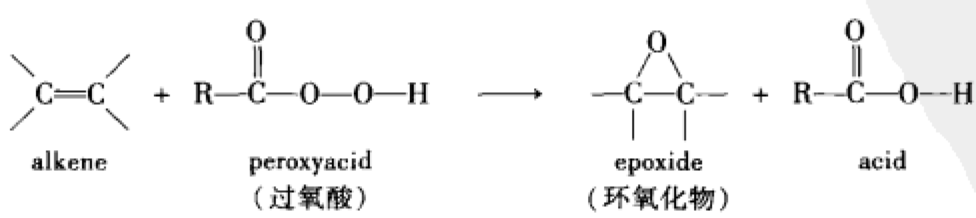
Such an explosion may be avoided by taking a few simple precautions. Ethers should be bought in small quantities, kept in tightly sealed containers, and used promptly. Any procedure requiring evaporation or distillation should use only peroxide-free ether. Any ether that might be contaminated with peroxides should be discarded or treated to destroy the peroxides.

16−7 Synthesis of Epoxides

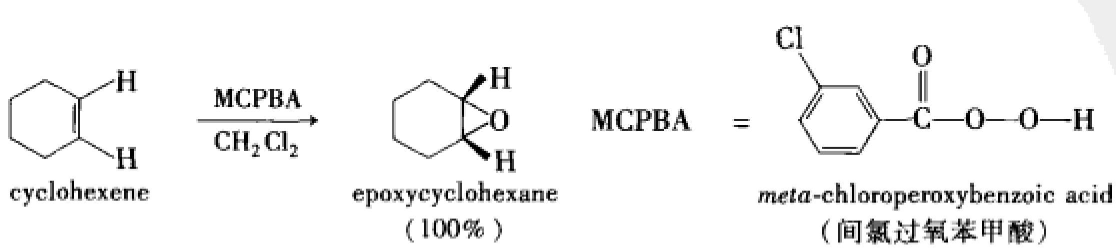
Epoxides are easily made from alkenes, and (unlike other ethers) they undergo a variety of useful synthetic reactions. For these reasons, epoxides are valuable synthetic intermediates. Here we review the epoxidation techniques already covered and consider in more detail the useful syntheses and reactions of epoxides.

16−7A Peroxyacid Epoxidation

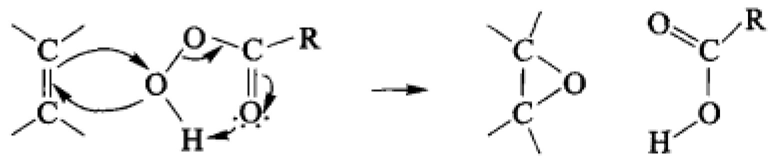
Peroxyacids (sometimes called *peracids*) are used to convert alkenes to epoxides. If the reaction takes place in aqueous acid, the epoxide opens to a glycol. Therefore, to make an epoxide, we use a weakly acidic peroxyacid that is soluble in aprotic solvents such as CH_2Cl_2. Because of its desirable solubility properties, *meta*-chloroperoxybenzoic acid (**MCPBA**) is often used for these epoxidations.



Example

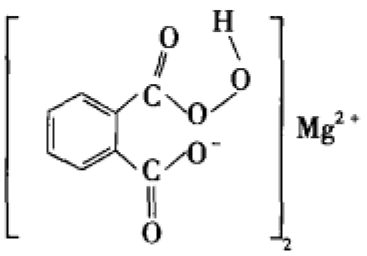


The epoxidation takes place in a one-step, **concerted reaction** that maintains the stereochemistry of any substituents on the double bond.

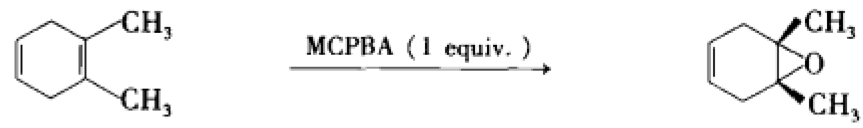


alkene peroxyacid epoxide acid

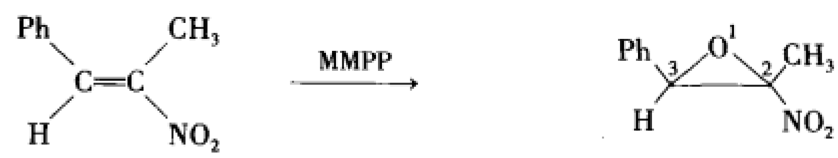
The peroxyacid epoxidation is quite general, with electron-rich double bonds reacting fastest. The following reactions are difficult transformations made possible by this selective, stereospecific epoxidation procedure. The second example uses magnesium monoperoxyphthalate (**MMPP**), a relatively stable water-soluble peroxyacid often used in large-scale epoxidations.



MMPP
(单过氧化邻苯二甲酸镁)



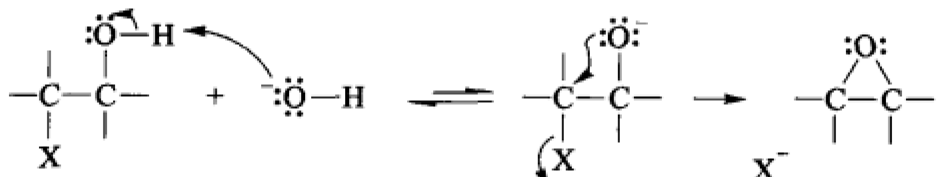
1,2-dimethyl-1,4-cyclohexadiene → *cis*-4,5-epoxy-4,5-dimethylcyclohexene
(顺-4,5-环氧-4,5-二甲基环己烯)



(*E*)-2-nitro-1-phenylpropene → (*E*)-2-methyl-2-nitro-3-phenyloxirane
[(*E*)-2-甲基-2-硝基-3-苯基环氧乙烷]

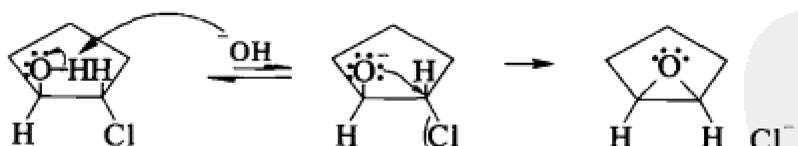
16-7B Base-Promoted Cyclization of Halohydrins

A second synthesis of epoxides and other cyclic ethers involves a variation of the Williamson ether synthesis. If an alkoxide ion and a halogen atom are located in the same molecule, the alkoxide may displace a halide ion and form a ring. Treatment of a halohydrin with a base leads to an epoxide through this internal S_N2 attack.



(X=Cl,Br,I)

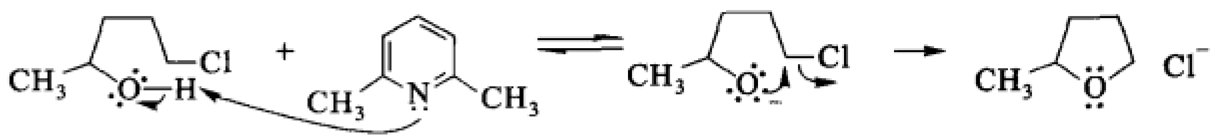
Example



trans-chlorohydrin alkoxide epoxide (环氧化物)
(50% overall)

Halohydrins are easily generated by treating alkenes with aqueous solutions of halogens. Bromine water and chlorine water add across double bonds with Markovnikov orientation.

This reaction can be used to synthesize cyclic ethers with larger rings. The difficulty lies in preventing the base (added to deprotonate the alcohol) from attacking and displacing the halide. 2,6-Lutidine, a bulky base that cannot easily attack a carbon atom, can be used to deprotonate the hydroxyl group to give a five-membered cyclic ether. Five-, six-, and seven-membered (and occasionally four-membered) cyclic ethers are formed this way.

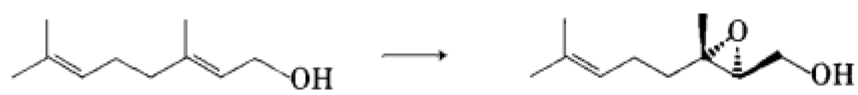


chloro-alcohol (卤代醇) + 2,6-lutidine (2,6-dimethylpyridine) (2,6-二甲基吡啶) ⇌ alkoxide (醇盐) → 2-methyltetrahydrofuran (85%) (2-甲基四氢呋喃)

PROBLEM 16−10

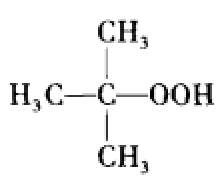
The 2001 Nobel Prize in chemistry was awarded to three organic chemists who have developed methods for catalytic asymmetric syntheses. An asymmetric (or enantioselective) synthesis is one that converts an achiral starting material into mostly one enantiomer of a chiral product. K. Barry Sharpless (The Scripps Research Institute) developed an asymmetric epoxidation of allylic alcohols that gives excellent chemical yields and greater than 90% enantiomeric excess.

The Sharpless epoxidation uses *tert*-butyl hydroperoxide, titanium (Ⅳ) isopropoxide, and a dialkyl tartrate ester as the reagents. The following epoxidation of geraniol is typical.

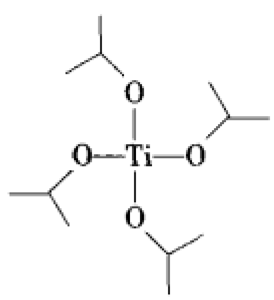


geraniol(牻牛儿醇;香叶醇) → 80% yield, >90% ee

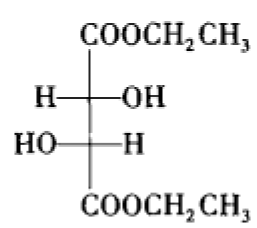
Reagents:



tert-butyl hydroperoxide (叔丁基氢过氧化物)



titanium (Ⅳ) isopropoxide (四异丙氧基钛)



diethyl L-tartrate (L-酒石酸二乙酯)

(a) Which of these reagents is most likely to be the actual oxidizing agent? That is, which reagent is reduced in the reaction? What is the likely function of the other reagents?

(b) When achiral reagents react to give a chiral product, that product is normally formed as a racemic mixture of enantiomers. How can the sharpless epoxidation give just one nearly pure enantiomer of the product?

(c) Draw the other enantiomer of the product. What reagents would you use if you wanted to epoxidize geraniol to give this other enantiomer?

16−8 Acid-Catalyzed Ring Opening of Epoxides

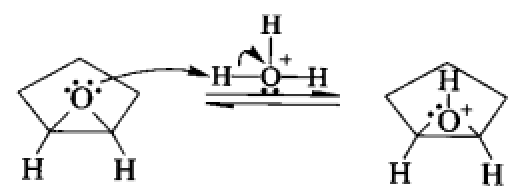
Epoxides are much more reactive than common dialkyl ethers because of the large strain energy (about 105 kJ/mol) associated with the three-membered ring. Unlike other ethers, epoxides react under both acidic and basic conditions. The products of acid-catalyzed opening depend primarily on the solvent used.

In Water Acid-catalyzed hydrolysis of epoxides gives glycols with anti stereochemistry. The mechanism of this hydrolysis involves protonation of oxygen (forming a good leaving group), followed by S_N2 attack by water. Anti stereochemistry results from the back-side attack of water on the protonated epoxide.

MECHANISM 16-2 Acid-Catalyzed Opening of Epoxides in Water

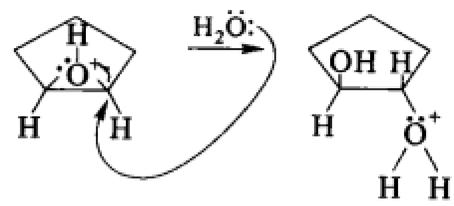
Epoxides open in acidic solutions to form glycols.

***Step 1*:** Protonation of the epoxide to form a strong electrophile.

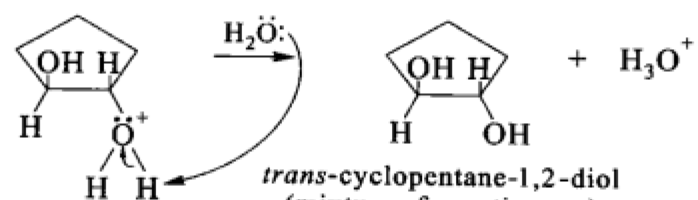


1,2-epoxycyclopentane

***Step 2*:** Water attacks and opens the ring.

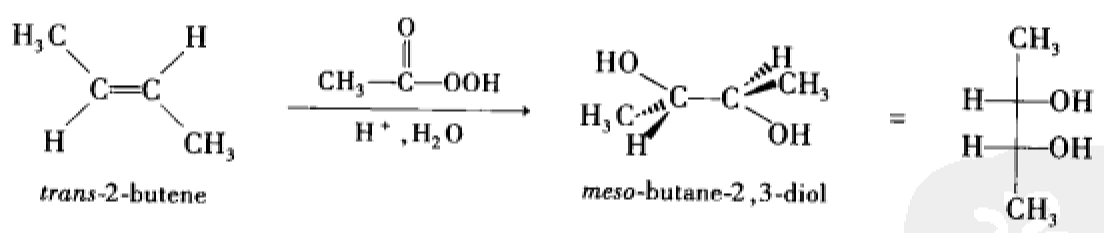


***Step 3*:** Deprotonation to give the diol.



trans-cyclopentane-1,2-diol (mixture of enantiomers)

Direct anti hydroxylation of an alkene (without isolation of the epoxide intermediate) is possible by using an acidic aqueous solution of a peroxyacid. As soon as the epoxide is formed, it hydrolyzes to the glycol. Peroxyacetic acid (CH_3CO_3H) and peroxyformic acid (HCO_3H) are often used for the anti hydroxylation of alkenes.

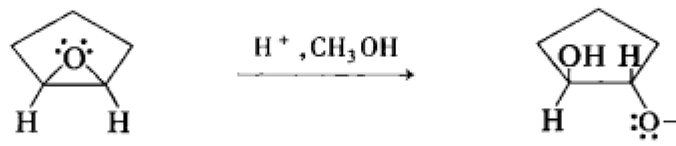


trans-2-butene *meso*-butane-2,3-diol

PROBLEM 16-11

Propose mechanisms for the epoxidation and ring-opening steps of the epoxidation and hydrolysis of *trans*-2-butene shown above. Predict the product of the same reaction with *cis*-2-butene.

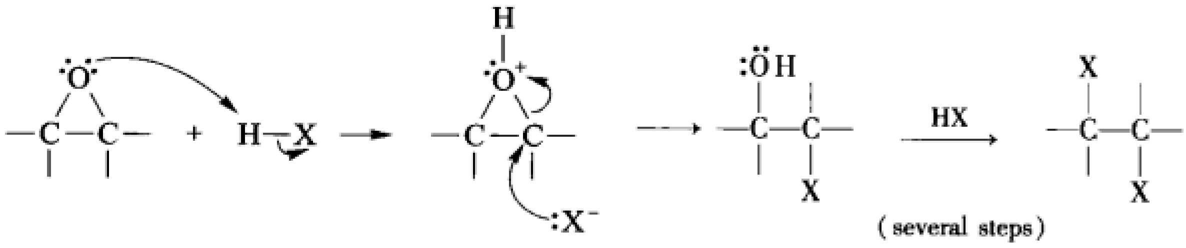
In Alcohols When the acid-catalyzed opening of an epoxide takes place with an alcohol as the solvent, a molecule of alcohol acts as the nucleophile. This reaction produces an alkoxy alcohol with anti stereochemistry. This is an excellent method for making compounds with ether and alcohol functional groups on adjacent carbon atoms. For example, the acid-catalyzed opening of 1,2-epoxycyclopentane in a methanol solution gives *trans*-2-methoxy-cyclopentanol.



1,2-epoxycyclopentane

trans-2-methoxyclopentanol (82%)
(mixture of enantiomers)

Using Hydrohalic Acids When an epoxide reacts with a hydrohalic acid (HCl, HBr, or HI), a halide ion attacks the protonated epoxide. This reaction is analogous to the cleavage of ethers by HBr or HI. The halohydrin initially formed reacts further with HX to give a 1,2-dihalide. This is rarely a useful synthetic reaction, because the 1,2-dihalide can be made directly from the alkene by electrophilic addition of X_2.



PROBLEM 16–12

When ethylene oxide is treated with anhydrous HBr gas, the major product is 1,2-dibromoethane. When ethylene oxide is treated with concentrated aqueous HBr, the major product is ethylene glycol. Use mechanisms to explain these results.

16–9 Base-Catalyzed Ring Opening of Epoxides

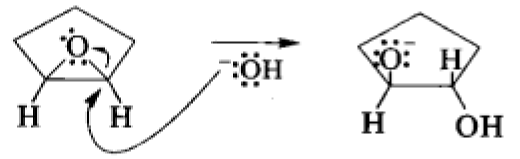
Most ethers do not undergo nucleophilic substitutions or eliminations under basic conditions, because an alkoxide ion is a poor leaving group. Epoxides have about 105 kJ/mol of ring strain that is released upon ring opening, however, and this strain is enough to compensate for the poor alkoxide leaving group.

The reaction of an epoxide with hydroxide ion leads to the same product as the acid-catalyzed opening of the epoxide: a 1,2-diol (glycol), with anti stereochemistry. In fact, either the acid-catalyzed or base-catalyzed reaction may be used to open an epoxide, but the acid-catalyzed reaction takes place under milder conditions. Unless there is an acid-sensitive functional group present, the acid-catalyzed hydrolysis is preferred.

MECHANISM 16–3 Base-Catalyzed Opening of Epoxides

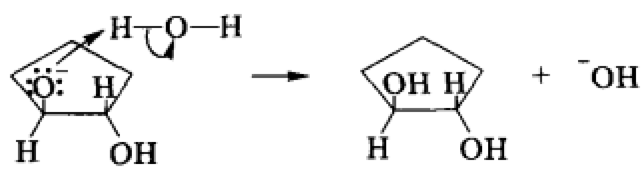
Strong bases and nucleophiles do not attack and cleave most ethers. Epoxides are more reactive, however, because opening the epoxide relieves the strain of the three-membered ring. Strong bases can attack and open epoxides, even though the leaving group is an alkoxide.

Step 1: A strong base attacks and opens the ring to an alkoxide.



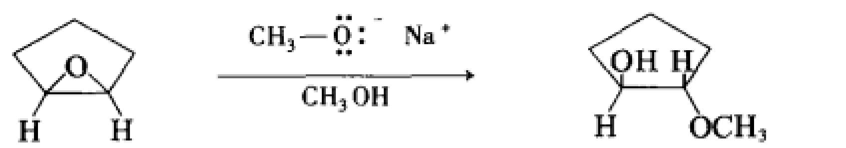
1,2-epoxycyclopentane
(1,2-环氧环戊烷)

Step 2: Protonation of the alkoxide gives the diol.



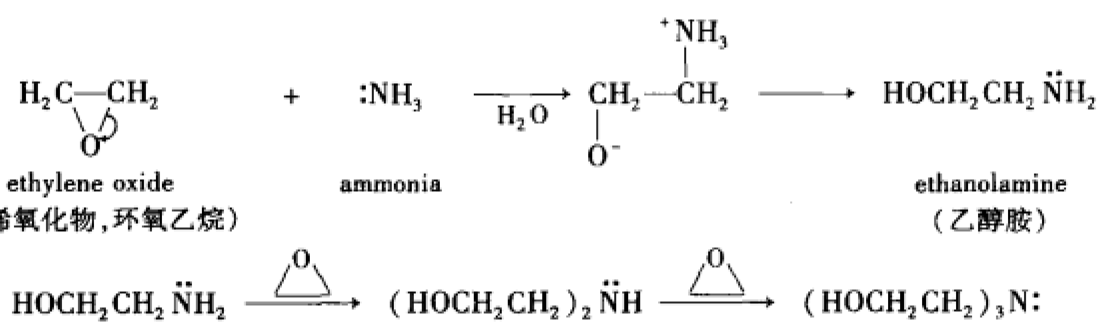
trans-cyclopentane-1,2-diol
(mixture of enantiomers)

Like hydroxide, alkoxide ions react with epoxides to form ring-opened products. For example, cyclopentene oxide reacts with sodium methoxide in methanol to give the same *trans*-2-methoxycyclopentanol produced in the acid-catalyzed opening in methanol.



cyclopentene oxide (环戊烯氧化物) → *trans*-2-methoxycyclopentanol (mixture of enantiomers)

Amines can also open epoxides. Ethylene oxide reacts with aqueous ammonia to give the important industrial reagent ethanolamine. The nitrogen atom in ethanolamine is still nucleophilic, and ethanolamine can react further to give diethanolamine and triethanolamine. Good yields of ethanolamine are achieved by using excess ammonia.



ethylene oxide (乙烯氧化物,环氧乙烷); ammonia; ethanolamine (乙醇胺)

ethanolamine; diethanolamine (二乙醇胺); triethanolamine (三乙醇胺)

PROBLEM 16-13

Propose a complete mechanism for the reaction of cyclopentene oxide with sodium methoxide in methanol.

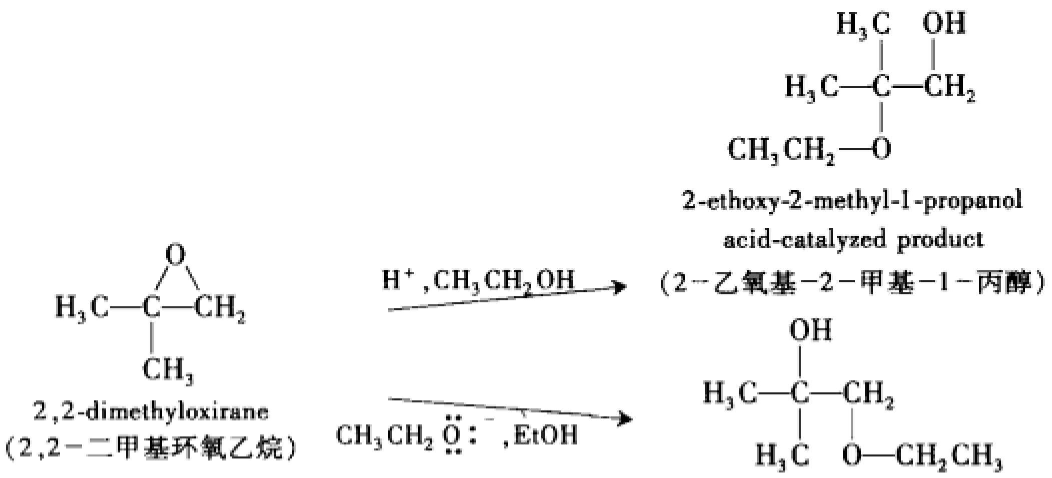
PROBLEM 16-14

Predict the major product when each reagent reacts with ethylene oxide.

(a) $NaOCH_2CH_3$ (sodium ethoxide) **(b)** $NaNH_2$ (sodium amide)
(c) NaSPh (sodium thiophenoxide) **(d)** $PhNH_2$ (aniline)
(e) KCN (potassium cyanide) **(f)** NaN_3 (sodium azide)

16-10 Orientation of Epoxide Ring Opening

Symmetrically substituted epoxides (such as cyclopentene oxide) give the same product in both the acid-catalyzed and base-catalyzed ring openings. An unsymmetrical epoxide gives different products under acid-catalyzed and base-catalyzed conditions, however.

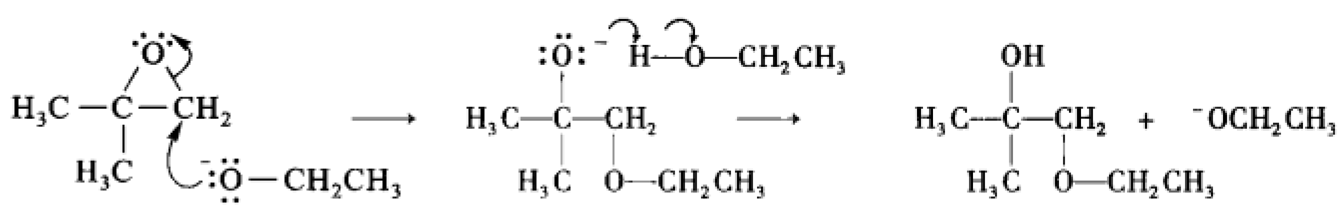


2,2-dimethyloxirane (2,2-二甲基环氧乙烷)

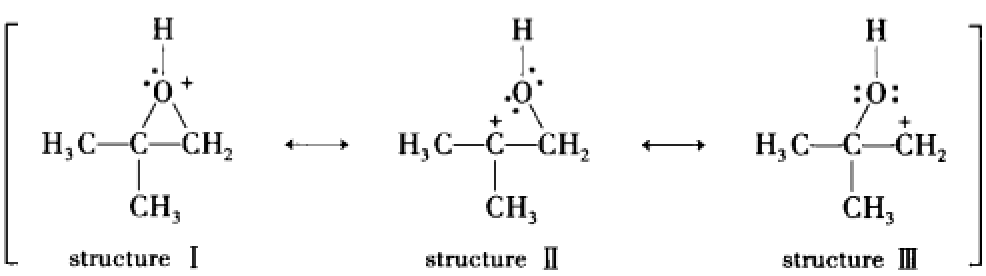
2-ethoxy-2-methyl-1-propanol acid-catalyzed product (2-乙氧基-2-甲基-1-丙醇)

1-ethoxy-2-methyl-2-propanol base-catalyzed product (1-乙氧基-2-甲基-2-丙醇)

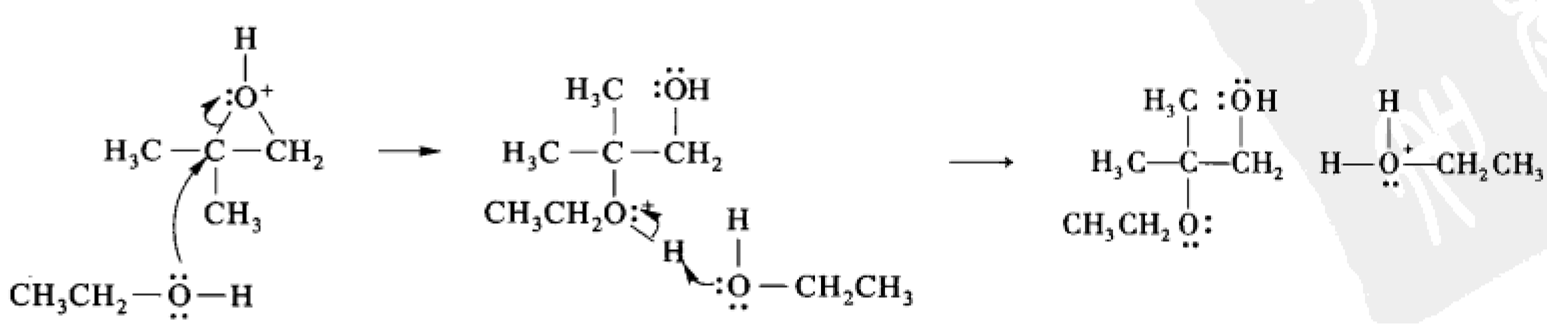
Under basic conditions, the alkoxide ion simply attacks the less hindered carbon atom in an S_N2 displacement.



Under acidic conditions, the alcohol attacks the protonated epoxide. It might seem that the alcohol would attack at the less hindered oxirane carbon, but this is not the case. In the protonated epoxide, there is a balancing act between ring strain and the energy it costs to put some of the positive charge on the carbon atoms. We can represent this sharing of positive charge by drawing the following three resonance structures:



Structure Ⅰ is the conventional structure for the protonated epoxide, while structures Ⅱ and Ⅲ show that the oxirane carbon atoms share part of the positive charge. The tertiary carbon bears a larger part of the positive charge, and it is more strongly electrophilic; that is, structure Ⅱ is more important than structure Ⅲ. The bond between the tertiary carbon and oxygen is weaker, implying a lower transition state energy for attack at the tertiary carbon. Attack by the weak nucleophile (ethanol in this case) is sensitive to the strength of the electrophile, and it occurs at the more electrophilic tertiary carbon.



This ring opening is similar to the opening of a bromonium ion in the formation of a bromohydrin and the opening of the mercurinium ion during oxymercuration. All three reactions involve the opening of an electrophilic three-membered ring by a weak nucleophile. Attack takes place at the more electrophilic carbon atom, which is usually the more substituted carbon because it can better support the positive charge. Most base-catalyzed epoxide openings, on the other hand, involve attack by a strong nucleophile at the less hindered carbon atom.

PROBLEM 16-15

Predict the major products of the following reactions, including stereochemistry where appropriate.

(**a**) 2,2-dimethyloxirane + $H^+/H_2{}^{18}O$ (oxygen-labeled water)

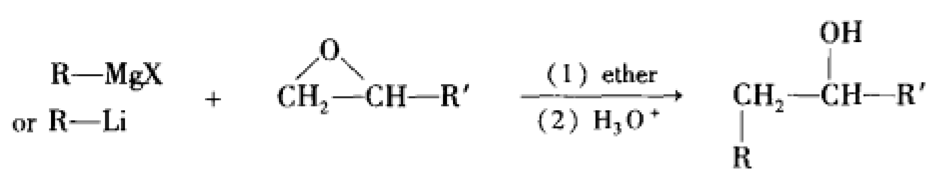
(**b**) 2,2-dimethyloxirane + $H^{18}O^-/H_2{}^{18}O$

(**c**) (*Z*)-2-ethyl-2,3-dimethyloxirane + CH_3O^-/CH_3OH

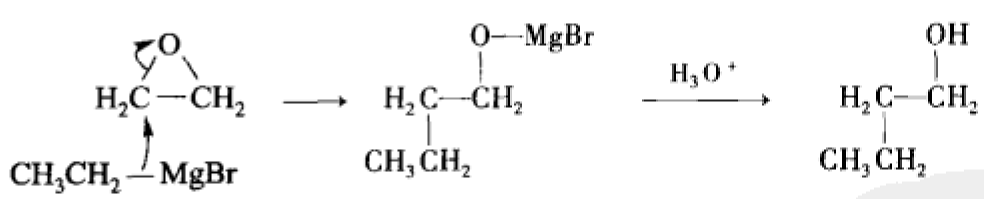
(**d**) (*Z*)-2-ethyl-2,3-dimethyloxirane + H^+/CH_3OH

16-11 Reactions of Epoxides with Grignard and Organolithium Reagents

Like other strong nucleophiles, Grignard and organolithium reagents attack epoxides to give (after hydrolysis) ring-opened alcohols.

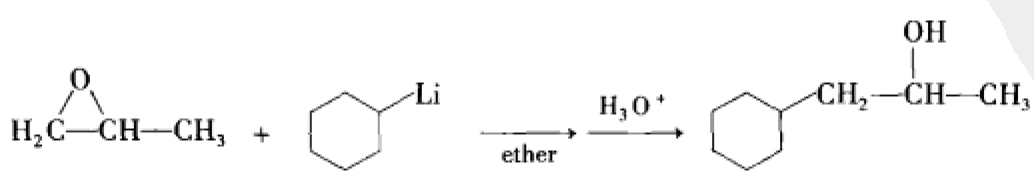


For example, ethylmagnesium bromide reacts with oxirane (ethylene oxide) to form the magnesium salt of 1-butanol.

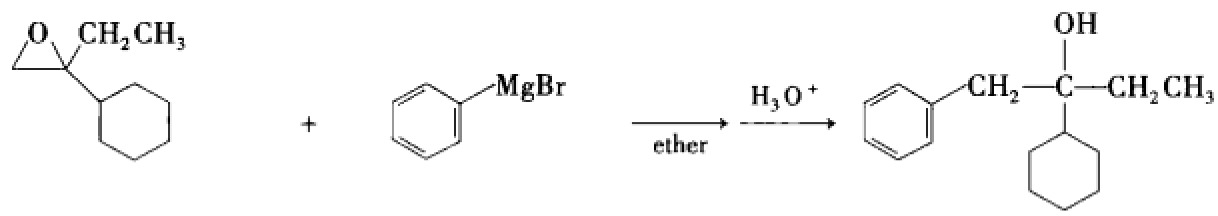


1-butanol

Substituted epoxides can be used in this reaction, with the carbanion attacking the less hindered epoxide carbon atom. This reaction works best if one of the oxirane carbons is unsubstituted, to allow an unhindered nucleophilic attack. Organolithium reagents (RLi) are more selective than Grignard reagents in attacking the less hindered epoxide carbon atom. Unless one carbon atom is very strongly hindered, Grignard reagents may give mixtures of products.



methyloxirane (甲基环氧乙烷) cyclohexyllithium (环己基锂) 1-cyclohexyl-2-propanol



2-cyclohexyl-2-ethyloxirane (2-环己基-2-乙基环氧乙烷) + phenylmagnesium bromide (苯基溴化镁) → 2-cyclohexyl-1-phenyl-2-butanol

PROBLEM 16-16

Give the expected products of the following reactions. Include a hydrolysis step where necessary.

(a) ethylene oxide + isopropylmagnesium bromide

(b) 2,2-dimethyloxirane + methyllithium

(c) cyclopentyloxirane + ethyllithium

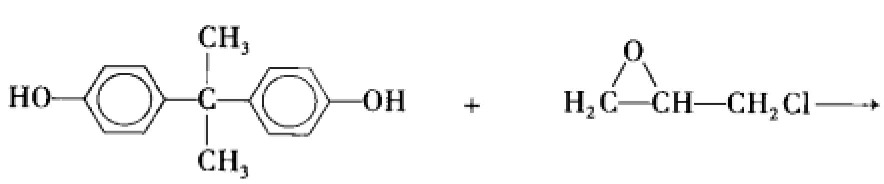
16-12 Epoxy Resins: The Advent of Modern Glues

The earliest glues were made of carbohydrates and proteins. Wheat paste uses the gluten in wheat, the sticky carbohydrate that holds bread together. Hide glue is a collagen-containing protein extract of animal hides, hooves, and tendons. Hide glue was used for wood and paper gluing for hundreds of years, and it is still used for fine musical instruments and other articles that must be readily taken apart without damaging the wood. Hide glue is water soluble, however, and the bond quickly fails in a damp environment. It does not fill gaps because it shrinks to a fraction of its wet volume as it dries. Glues based on casein (a milk protein) were developed to give a stronger, water-resistant bond. A casein glue (such as Elmer's®) gives a bond as strong as most woods, and it resists water for hours before it softens. But it does not fill gaps well, and it works poorly with metals and plastics.

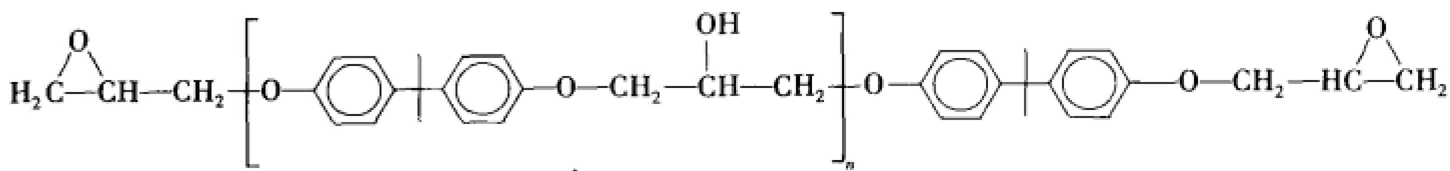
Imagine a glue that does not shrink at all as it hardens; it fills gaps perfectly so that pieces don't need to be fitted closely. It holds forever in water, is at least as strong as wood and plastic, and sticks to anything: wood, metal, plastic, etc. It lasts forever on the shelf without hardening, yet hardens quickly once the pieces are in place. It can be made runny so it fills tiny voids, or thick and pasty so it stays in place while it hardens.

This ideal glue was only a dream until the development of epoxy adhesives. Epoxies polymerize in place, so they match the shape of the joint perfectly and adhere to microscopic irregularities in the surfaces. There is no solvent to evaporate, so there is no shrinkage. Epoxies are bonded by ether linkages, so they are unaffected by water. Epoxies use a prepolymer that can be made as runny or as gummy as desired, and they use a hardening agent that can be modified to control the curing time. In the absence of the hardening agent, they have a long shelf life.

The most common epoxy resins use a prepolymer made from *bisphenol A* and epichlorohydrin.

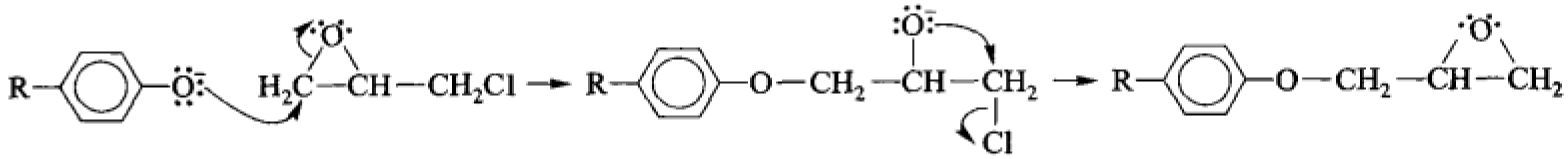


bisphenol A (双酚A) + epichlorohydrin (3-氯-1,2-环氧丙烷,表氯醇) →

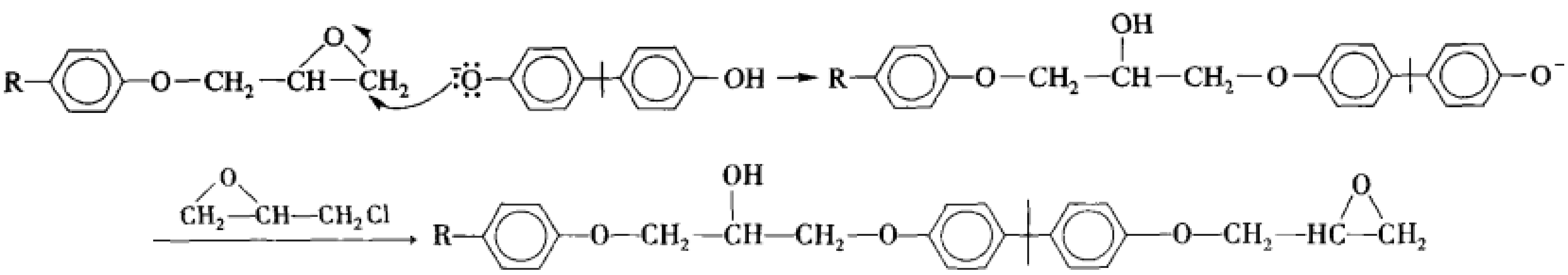


prepolymer

Under base-catalyzed conditions, the anion of bisphenol A opens the epoxide of epichlorohydrin to give an alkoxide that snaps shut on the other and, forming another epoxide.



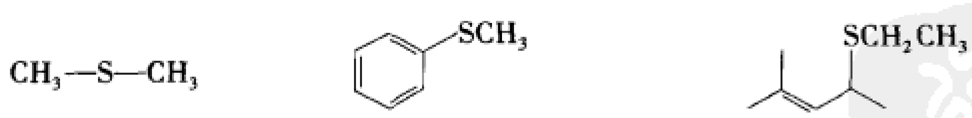
This second epoxide reacts with another molecule of bisphenol A. Each molecule of bisphenol A can also react with two molecules of epichlorohydrin.



With exactly equal amounts of bisphenol A and epichlorohydrin, this polymerization would continue until the polymer chains were very long and the material would be a solid polymer. In making epoxy resins, however, excess epichlorohydrin is added to form short chains with epichlorohydrins on both ends. More epichlorohydrin gives shorter chains and a runny prepolymer. Less epichlorohydrin gives longer chains (containing up to 25 epichlorohydrin/bisphenol A units) and a more viscous prepolymer.

16-13 Sulfides (Thioethers)

Sulfides are also called **thioethers** because they are the sulfur analogues of ethers. Like thiols, sulfides have strong characteristic odors: The odor of dimethyl sulfide is reminiscent of oysters that have been kept in the refrigerator for too long. Sulfides are named like ethers, with "sulfide" replacing "ether" in the common names. In the IUPAC (alkoxy alkane) names, "alkylthio" replaces "alkoxy."



dimethyl sulfide (二甲基硫醚) methyl phenyl sulfide (甲基苯基硫醚) 4-ethylthio-2-methyl-2-pentene (4-乙硫基-2-甲基-2-戊烯)

Sulfides are easily synthesized by the Williamson ether synthesis, using a thiolate ion as the nucleophile.

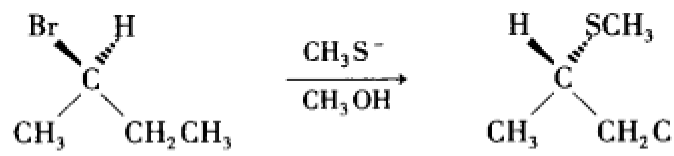
ethanethiolate (乙硫醇盐) 1-bromopropane ethyl propyl sulfide (乙基丙基硫醚)

Thiols are more acidic than water. Therefore, thiolate ions are easily generated by treating thiols with aqueous sodium hydroxide.

$$\underset{pK_a = 10.5}{CH_3CH_2{-}SH} + Na^+\ ^-OH \rightleftharpoons \underset{\text{sodium ethanethiolate}}{CH_3CH_2{-}S^-\ ^+Na} + \underset{pK_a = 15.7}{H_2O}$$

（乙硫醇钠）

Because sulfur is larger and more polarizable than oxygen, thiolate ions are even better nucleophiles than alkoxide ions. Thiolates are such effective nucleophiles that secondary alkyl halides often react to give good yields of S_N2 products.



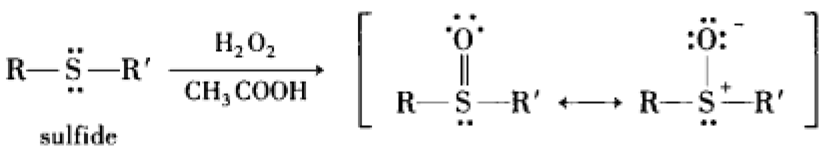
(R)-2-bromobutane → (S)-2-(methylthio)butane

(S)-2-(甲硫基)丁烷

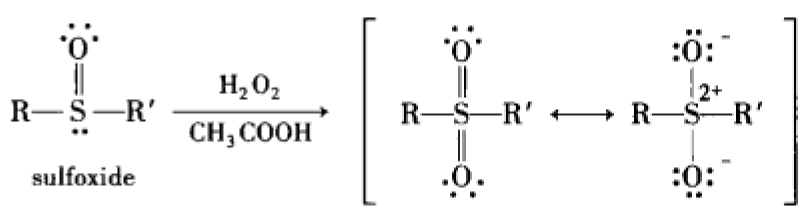
PROBLEM 16-17

Show how you would synthesize butyl isopropyl sulfide using 1-butanol, 2-propanol, and any solvents and reagents you need.

Sulfides are much more reactive than ethers. In a sulfide, sulfur's valence is not necessarily filled: Sulfur can form additional bonds with other atoms. Sulfur forms particularly strong bonds with oxygen, and sulfides are easily oxidized to sulfoxides and sulfones. **Sulfoxides** and **sulfones** are drawn using either hypervalent double-bonded structures or formally charged single-bonded structures as shown here.

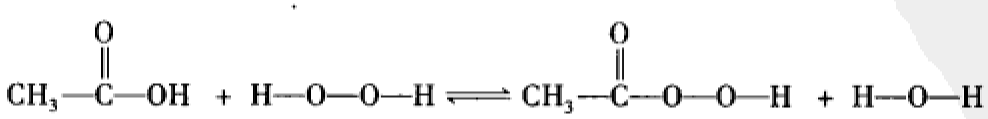


sulfide（硫醚） sulfoxide（亚砜）



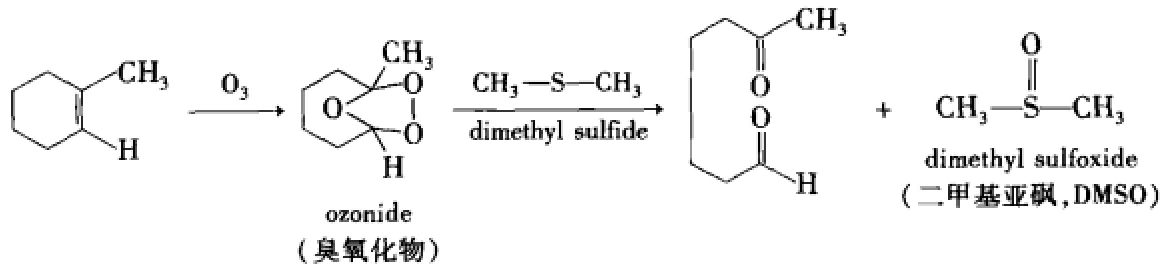
sulfoxide sulfone（砜）

The hydrogen peroxide/acetic acid combination is a good oxidant for sulfides. One equivalent of peroxide gives the sulfoxide, and a second equivalent further oxidizes the sulfoxide to the sulfone. This reagent combination probably reacts via the peroxyacid, which is formed in equilibrium with hydrogen peroxide.

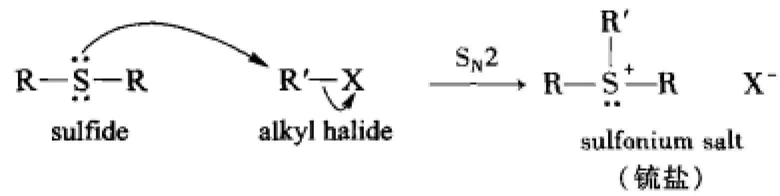


acid peroxyacid（过氧酸）

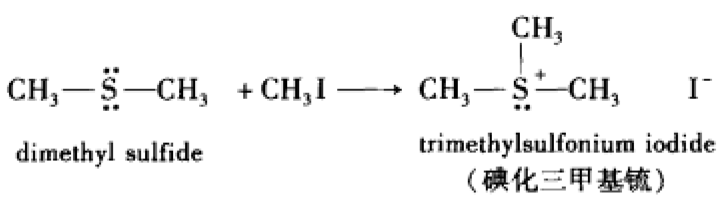
Because they are easily oxidized, sulfides are often used as mild reducing agents. For example, we have used dimethyl sulfide to reduce the potentially explosive ozonides that result from ozonolysis of alkenes.



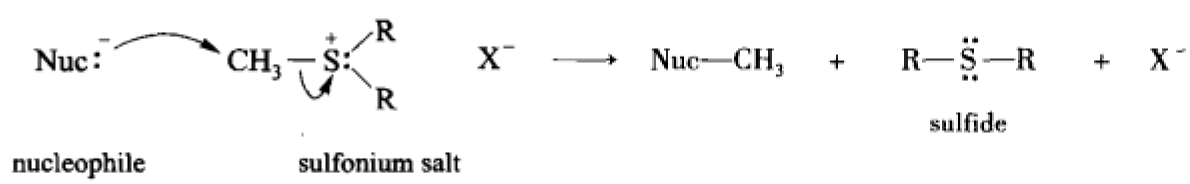
Sulfur compounds are more nucleophilic than the corresponding oxygen compounds, because sulfur is larger and more polarizable and its electrons are less tightly held in orbitals that are farther from the nucleus. Although ethers are weak nucleophiles, sulfides are relatively strong nucleophiles. Sulfides attack unhindered alkyl halides to give **sulfonium salts**.



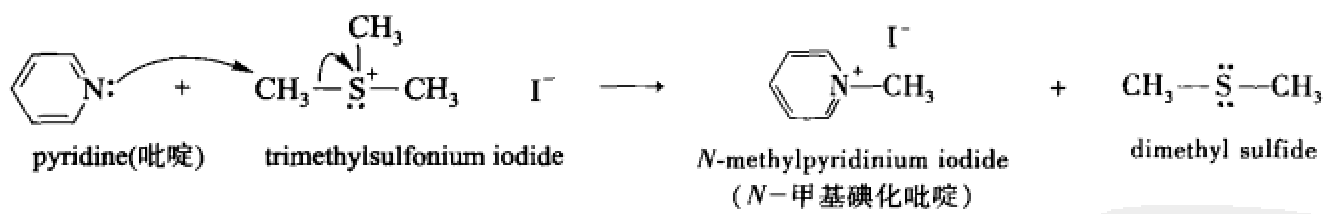
Example



Sulfonium salts are good alkylating agents because the leaving group is an uncharged sulfide. Sulfur's polarizability enhances partial bonding in the transition state, lowering its energy.



Example



Summary in Chinese

本章概要

一、醚的结构

醚键(C—O—C)是醚类化合物的结构特征,其中氧原子是以 sp^3 杂化状态(芳醚和烯醚为 sp^2 杂化)分别与两个烃基的碳原子形成两个 σ 键,氧原子另外两个 sp^3 轨道中各有一对电子。一般脂醚的∠COC键角约为110°。

二、醚的物理性质

醚不能形成分子间氢键,沸点与相对分子质量相似的烃相近;醚与水能形成氢键,在水中有一定的溶

解度。由于醚的偶极矩较大,化学性质不活泼,沸点低,所以常用做极性溶剂。

三、醚的制备

1. Williamson 法合成醚（the Williamson ether synthesis）

$$R{-}\ddot{\underset{\cdot\cdot}{O}}{:}^{-} + R'X \longrightarrow R{-}\ddot{\underset{\cdot\cdot}{O}}{-}R' + X^{-}$$

X = Cl, Br, I, OTs 等。

☆ 必须是伯卤代烃,仲、叔卤代烃容易发生消除反应。

2. 醇分子间脱水（intermolecular dehydration of alcohols）

$$2ROH \xrightleftharpoons{H^{+}} R{-}O{-}R + H_2O$$

☆ 必须是伯醇,用于醇的工业制备。

四、醚的化学性质

一般情况下,脂肪族饱和醚对氧化剂、还原剂都不发生作用,而且在碱性介质中尤为稳定。由于醚的氧原子上有未共用的电子对,具有一定的碱性,可以与强酸发生化学反应,也可以与 RMgX、BH_3 等形成络合物。

1. 与 HX 反应——醚键的断裂（cleavage of ethers）:

$$R{-}O{-}R' \xrightarrow{\text{过量 HX}} R{-}X + R'{-}X$$

$$Ar{-}O{-}R \xrightarrow[X = Br, I]{\text{过量 HX}} Ar{-}OH + R{-}X$$

☆ 类似于 S_N2 反应机理;HX 反应活性为 HI > HBr≫HCl。

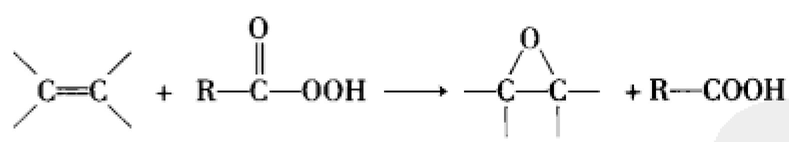
2. 醚的自动氧化(autoxidation of ethers):

$$R{-}O{-}CH_2R' \xrightarrow[\text{慢}]{\text{过量 } O_2} R{-}O{-}\underset{}{\overset{OOH}{\overset{|}{C}}}HR' + R{-}O{-}O{-}CH_2R'$$

☆ 过氧化物容易爆炸,蒸馏醚前应确认醚中无过氧化物;醚的存放应避光,密封存放于阴凉处。

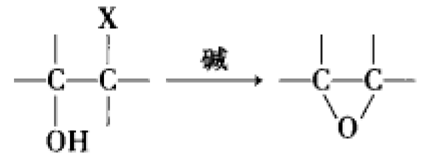
五、环醚的制备

1. 烯烃与过氧酸的反应:



☆ **常用的过氧酸:间氯过氧苯甲酸(MCPBA)、单过氧化邻苯二甲酸镁(MMPP)等。**

2. 卤代醇脱卤化氢:

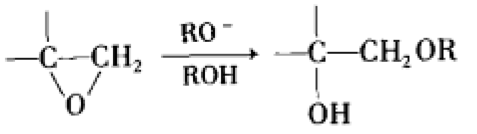


X = Cl, Br, I, OTs 等

六、环氧化合物(环醚)的化学性质

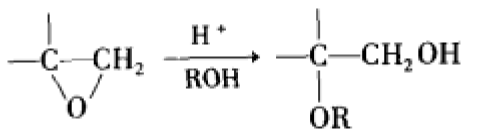
环氧化合物可以在酸或者碱催化下,与亲核试剂发生类似 S_N1 或 S_N2 机理的开环加成反应。

1. 碱催化开环(base-catalyzed opening):



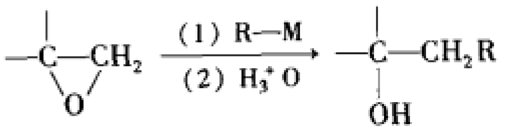
☆ 类似于 S_N2 机理;亲核试剂(Nuc^-)与取代基少的碳原子成键。

2. 酸催化开环(acid-catalyzed opening):



☆ 类似于 S_N1 机理;亲核试剂与取代基多的碳原子成键。

3. 与有机金属化合物反应:



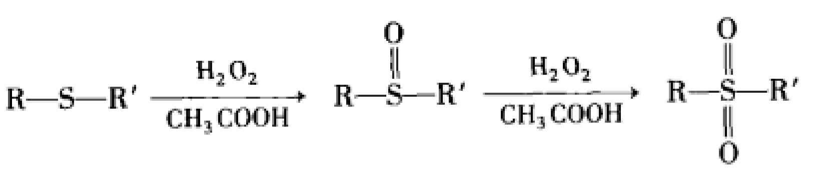
M = Li or MgX

☆ 类似于 S_N2 机理;R 与取代基少的碳原子成键;该反应用于制备碳链增长的醇。

七、硫醚的结构与性质

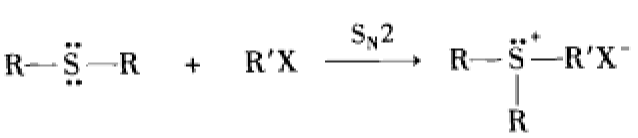
硫醚的结构、性质与醚相似,其化学性质较稳定。但由于硫原子的半径大、电负性小,因此,硫醚具有较明显的碱性、亲核性及易于氧化的特性。

1. 氧化反应:



☆ 利用这一性质,硫醚常被用做温和的还原剂。

2. 亲核反应(nucleophilic reaction):



☆ 用于制备锍盐,锍盐是很好的烷基化试剂。

Essential Problem-Solving Skills in Chapter 16

1. Predict relative boiling points and solubilities of ethers.
2. Explain how ether solvents stabilize electrophilic reagents and why they are compatible with organometallic reagents.
3. Determine the structures of ethers from their spectra, and explain their characteristic absorptions and fragmentations.
4. Devise efficient laboratory syntheses of ethers and epoxides, including
   (a) The Williamson ether synthesis
   (b) Alkoxymercuration-demercuration
   (c) Peroxyacid epoxidation

(d) Base-promoted cyclization of halohydrins

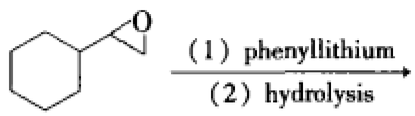
5. Predict the products of reactions of ethers and epoxides, including
   (a) Cleavage and autoxidation of ethers
   (b) Acid- and base-promoted opening of epoxides
   (c) Reactions of epoxides with organometallic reagents
6. Use your knowledge of the mechanisms of ether and epoxide reactions to propose mechanisms and products for similar reactions you have never seen before.

Study Problems

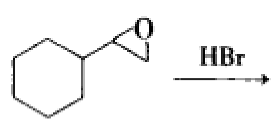
16–18 Briefly define each term, and give an example.

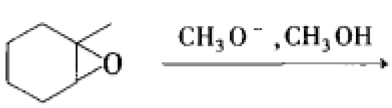
(a) autoxidation (b) Williamson ether synthesis (c) alkoxymercuration-demercuration
(d) heterocyclic compound (e) epoxidation (f) concerted reaction
(g) unsymmetrical ether (h) crown ether (i) sulfonium salt

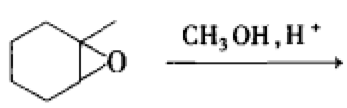
16–19 Predict the products of the following reactions.

(a) *sec*-butyl isopropyl ether + concd. HBr, heat
(b) *t*-butyl ethyl ether + concd. HBr, heat
(c) di-*n*-butyl ether + hot concd. NaOH
(d) di-*n*-butyl ether + Na metal
(e) ethoxybenzene + concd. HI, heat
(f) 1,2-epoxyhexane + H^+, CH_3OH
(g) *trans*-2,3-epoxyoctane + H^+, H_2O
(h) propylene oxide + methylamine (CH_3NH_2)
(i) potassium *t*-butoxide + *n*-butyl bromide
(j) 

(k)

(l) 

(m) 

(n) 

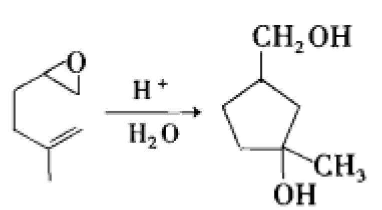
16–20 (A true story.) An inexperienced graduate student moved into a laboratory and began work. He needed some diethyl ether for a reaction, so he opened an old, rusty 1-gallon can marked "ethyl ether" and found there was half a gallon left. To purify the ether, the student set up a distillation apparatus, started a careful distillation, and went to the stockroom for the other reagents he needed. While he was at the stockroom, the student heard a muffled "boom". He quickly returned to his lab to find a worker from another laboratory putting out a fire. Most of the distillation apparatus was embedded in the ceiling.

(a) Explain what probably happened.
(b) Explain how this near-disaster might have been prevented.

16–21 (a) Show how you would synthesize the pure (R) enantiomer of 2-butyl methyl sulfide starting with pure (R)-2-butanol and any reagents you need.
(b) Show how you would synthesize the pure (S) enantiomer of the product.

16–22 (a) Predict the values of m/z and the structures of the most abundant fragments you would observe in the mass spectrum of di-*n*-propyl ether.
(b) Give logical fragmentations to account for the following ions observed in the mass spectrum of 2-methoxypentane: 102, 87, 71, 59, 31.

16–23 The following reaction resembles the acid-catalyzed cyclization of squalene oxide. Propose a mechanism for this reaction.



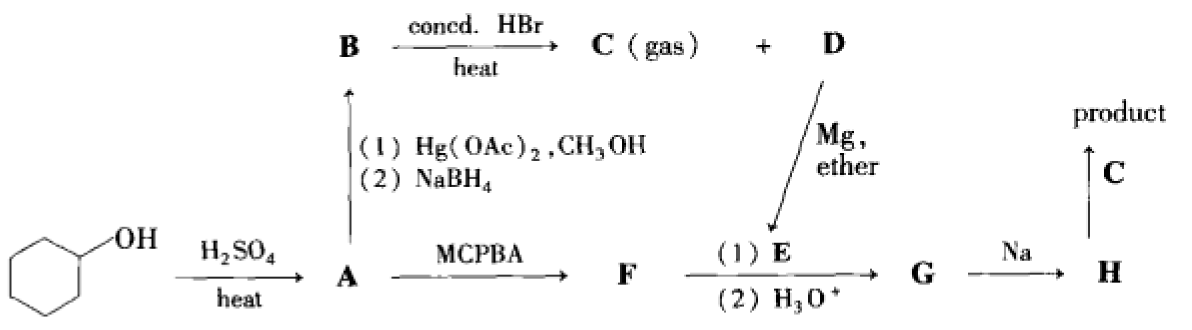
16–24 Show how you would accomplish the following synthetic transformations in good yield.

(**a**) 1-hexene → 1-phenyl-2-hexanol

(**b**) 1-hexene → 1-methoxy-2-hexanol

(**c**) 1-hexene → 2-methoxy-1-hexanol

16–25 Give the structures of intermediates **A** through **H** in the following synthesis of *trans*-1-cyclohexyl-2-methoxycyclohexane.



16–26 (Another true story.) An organic lab student carried out the reaction of methylmagnesium iodide with acetone (CH_3COCH_3), followed by hydrolysis. During the distillation to isolate the product, she forgot to mark the vials she used to collect the fractions. She turned in a product of formula $C_4H_{10}O$ that boiled at 35 ℃. The IR spectrum showed only a weak O—H stretch around 3300 cm^{-1}, and the mass spectrum showed a base peak at *m/z* 59. The NMR spectrum showed a quartet ($J = 7$ Hz) of area 2 at δ3.5 and a triplet ($J = 7$ Hz) of area 3 at δ1.3. Propose a structure for this product, explain how it corresponds to the observed spectra, and suggest how the student isolated this compound.

16–27 Show how you would synthesize the following ethers in good yield from the indicated starting materials and any additional reagents needed.

(**a**) cyclopentyl *n*-propyl ether from cyclopentanol and 1-propanol

(**b**) *n*-butyl phenyl ether from phenol and 1-butanol

(**c**) 2-methoxydecane from a decene

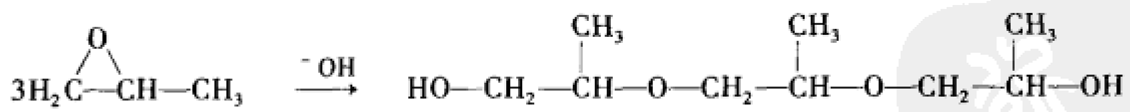
(**d**) 1-methoxydecane from a decene

(**e**) 1-ethoxy-1-methylcyclohexane from 1-methylcyclohexene

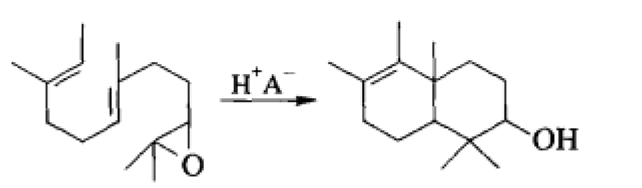
(**f**) *trans*-2,3-epoxyoctane from *trans*-2-octene

16–28 There are two different ways of making 2-ethoxyoctane from 2-octanol using the Williamson ether synthesis. When pure (–)-2-octanol of specific rotation –8.24° is treated with sodium metal and then ethyl iodide, the product is 2-ethoxyoctane with a specific rotation of –15.6°. When pure (–)-2-octanol is treated with tosyl chloride and pyridine and then with sodium ethoxide, the product is also 2-ethoxyoctane. Predict the rotation of the 2-ethoxyoctane made using the tosylation/sodium ethoxide procedure, and propose a detailed mechanism to support your prediction.

16–29 Under base-catalyzed conditions, several molecules of propylene oxide can react to give short polymers. Propose a mechanism for the base-catalyzed formation of the following trimer.



16–30 Under the right conditions, the following acid-catalyzed double cyclization proceeds in remarkably good yields. Propose a mechanism. Does this reaction resemble a biological process you have seen?



16–31 Propylene oxide is a chiral molecule. Hydrolysis of propylene oxide gives propylene glycol, another chiral molecule.

(**a**) Draw the enantiomers of propylene oxide.

(**b**) Propose a mechanism for the acid-catalyzed hydrolysis of pure (*R*)-propylene oxide.

(c) Propose a mechanism for the base-catalyzed hydrolysis of pure (*R*)-propylene oxide.

(d) Explain why the acid-catalyzed hydrolysis of optically active propylene oxide gives a product with a rotation opposite that of the product of the base-catalyzed hydrolysis.

Chapter 17

Aromatic Compounds

17–1 Introduction: The Discovery of Benzene

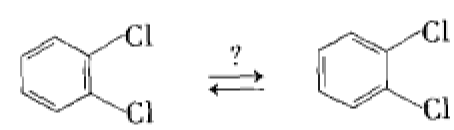
In 1825, Michael Faraday isolated a pure compound of boiling point 80 ℃ from the oily mixture that condensed from illuminating gas, the fuel burned in gaslights. Elemental analysis showed an unusually small hydrogen-to-carbon ratio of 1 : 1, corresponding to an empirical formula of CH. Faraday named the new compound "bicarburet of hydrogen." Eilhard Mitscherlich synthesized the same compound in 1834 by heating benzoic acid, isolated from gum benzoin, in the presence of lime. Like Faraday, Mitscherlich found that the empirical formula was CH. He also used a vapor-density measurement to determine a molecular weight of about 78, for a molecular formula of C_6H_6. Since the new compound was derived from gum benzoin, he named it benzin, now called *benzene*.

Many other compounds discovered in the nineteenth century seemed to be related to benzene. These compounds also had low hydrogen-to-carbon ratios as well as pleasant aromas, and they could be converted to benzene or related compounds. This group of compounds was called **aromatic** because of their pleasant odors. Other organic compounds, without these properties, were called **aliphatic**, meaning "fatlike." As the unusual stability of aromatic compounds was investigated, the term *aromatic* came to be applied to compounds with this stability, regardless of their odors.

17–2 The Structure and Properties of Benzene

The Kekulé Structure In 1866, Friedrich Kekulé proposed a cyclic structure for benzene with three double bonds. Considering that multiple bonds had been proposed only recently (1859), the cyclic structure with alternating single and double bonds was considered somewhat bizarre.

The **Kekulé structure** has its shortcomings, however. For example, it predicts two different 1,2-dichlorobenzenes, but only one is known to exist. Kekulé suggested (incorrectly) that a fast equilibrium interconverts the two isomers of 1,2-dichlorobenzene.

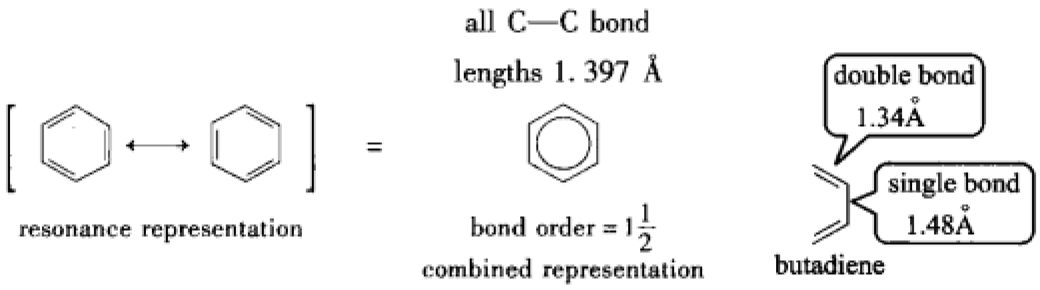


1,2-dichlorobenzene

The Resonance Representation The resonance picture of benzene is a natural extension of Kekulé's hypothesis. In a Kekulé structure, the C—C single bonds would be longer than the double bonds. Spectroscopic methods

have shown that the benzene ring is planar and all the bonds are the same length (1.397 Å). Because the ring is planar and the carbon nuclei are positioned at equal distances, the two Kekulé structures differ only in the positioning of the pi electrons.

Benzene is actually a resonance hybrid of the two Kekulé structures. This representation implies that the pi electrons are delocalized, with a bond order of $1\frac{1}{2}$ between adjacent carbon atoms. The carbon-carbon bond lengths in benzene are shorter than typical single-bond lengths, yet longer than typical double-bond lengths.



The resonance-delocalized picture explains most of the structural properties of benzene and its derivatives—the *benzenoid* aromatic compounds. Because the pi bonds are delocalized over the ring, we often inscribe a circle in the hexagon rather than draw three localized double bonds. This representation helps us remember there are no localized single or double bonds, and it prevents us from trying to draw supposedly different isomers that differ only in the placement of double bonds in the ring. We often use Kekulé structures in drawing reaction mechanisms, however, to show the movement of individual pairs of electrons.

PROBLEM 17-1

Write Lewis structures for the Kekulé representations of benzene. Show all the valence electrons.

Using this resonance picture, we can draw a more realistic representation of benzene (Figure 17-1). Benzene is a ring of six sp^2-hybrid carbon atoms, each bonded to one hydrogen atom. All the carbon-carbon bonds are the same length, and all the bond angles are exactly 120°. Each sp^2 carbon atom has an unhybridized p orbital perpendicular to the plane of the ring, and six electrons occupy this circle of p orbitals.

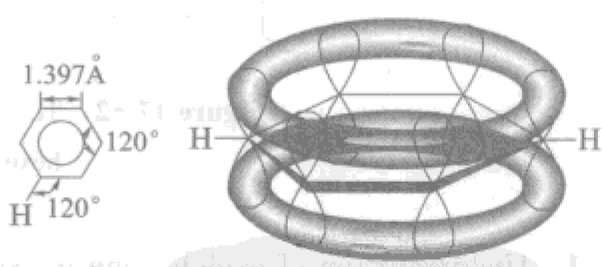


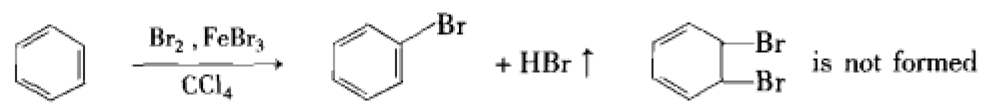
Figure 17-1 The Structure of Benzene.

At this point, we can define an **aromatic compound** to be a cyclic compound containing some number of conjugated double bonds and having an unusually large resonance energy. Using benzene as the example, we will consider how aromatic compounds differ from aliphatic compounds. Then we will discuss why an aromatic structure confers extra stability and how we can predict aromaticity in some interesting and unusual compounds.

The Unusual Reactions of Benzene Benzene is actually much more stable than we would expect from the simple resonance-delocalized picture. Both the Kekulé structure and the resonance-delocalized picture show that benzene is a cyclic conjugated triene. We might expect benzene to undergo the typical reactions of polyenes. In fact, its reactions are quite unusual. For example, an alkene decolorizes potassium permanganate by reacting to form a glycol. The purple permanganate color disappears, and a precipitate of manganese dioxide forms. When permanganate is added to benzene, however, no reaction occurs.

Most alkenes decolorize solutions of bromine in carbon tetrachloride. The red bromine color disappears as bromine adds across the double bond. When bromine is added to benzene, no reaction occurs, and the red bromine color remains.

Addition of a catalyst such as ferric bromide to the mixture of bromine and benzene causes the bromine color to disappear slowly. HBr gas is evolved as a byproduct, but the expected *addition* of Br_2 does not take place. Instead, the organic product results from *substitution* of a bromine atom for a hydrogen, and all three double bonds are retained.



The Unusual Stability of Benzene Benzene's reluctance to undergo typical alkene reactions suggests that it must be unusually stable. By comparing molar heats of hydrogenation, we can get a quantitative idea of its stability. Benzene, cyclohexene, and the cyclohexadienes all hydrogenate to form cyclohexane. Figure 17-2 shows how the experimentally determined heats of hydrogenation are used to compute the resonance energies of 1,3-cyclohexadiene and benzene, based on the following reasoning:

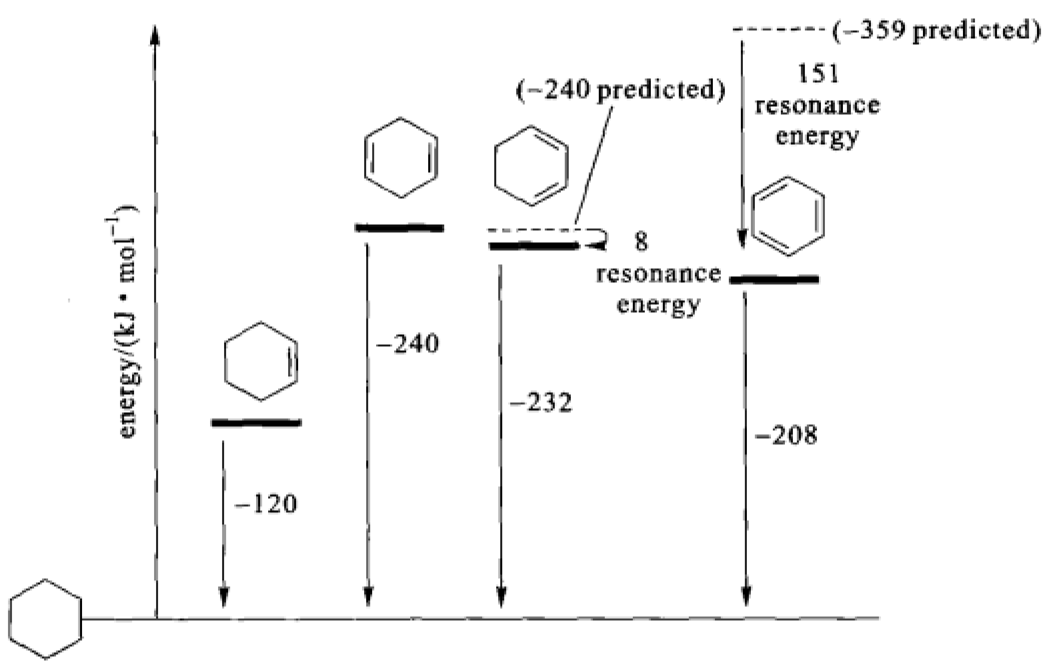


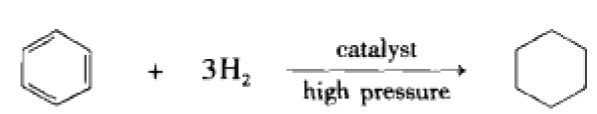
Figure 17-2 The molar heats of hydrogenation and the relative energies of cyclohexene, 1,4-cyclohexadiene, 1,3-cyclohexadiene, and benzene.

1. Hydrogenation of cyclohexene is exothermic by 120 kJ/mol.

2. Hydrogenation of 1,4-cyclohexadiene is exothermic by 240 kJ/mol, about twice the heat of hydrogenation of cyclohexene. The resonance energy of the isolated double bonds in 1,4-cyclohexadiene is about zero.

3. Hydrogenation of 1,3-cyclohexadiene is exothermic by 232 kJ/mol, about 8 kJ less than twice the value for cyclohexene. A resonance energy of 8 kJ is typical for a conjugated diene.

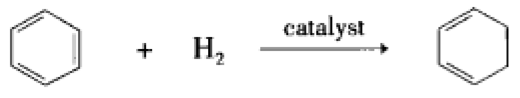
4. Hydrogenation of benzene requires higher pressures of hydrogen and a more active catalyst. This hydrogenation is exothermic by 208 kJ/mol, about 151 kJ less than 3 times the value for cyclohexene.



$\Delta H^\ominus$ = 208 kJ/mol
3 × cyclohexene = 359 kJ/mol
resonance energy = 151 kJ/mol

The huge 151 kJ/mol resonance energy of benzene cannot be explained by conjugation effects alone. The

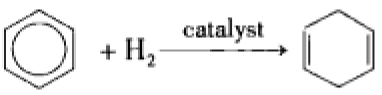
heat of hydrogenation for benzene is actually smaller than that for 1,3-cyclohexadiene. The hydrogenation of the *first* double bond of benzene is endothermic, the first endothermic hydrogenation we have encountered. In practice, this reaction is difficult to stop after the addition of 1 mole of H_2 because the product (1,3-cyclohexadiene) hydrogenates more easily than benzene itself. Clearly, the benzene ring is exceptionally unreactive.

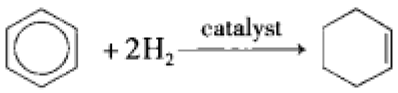


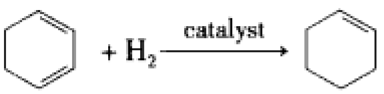
	$\Delta H^{\ominus}_{\text{hydrogenation}}$
benzene:	−208 kJ/mol
1,3-cyclohexadiene:	−232 kJ/mol
$\Delta H^{\ominus}$ =	+24 kJ/mol

PROBLEM 17-2

Using the information in Figure 17-2, calculate the values of $\Delta H^{\ominus}$ for the following reactions:

(a) 

(b) 

(c) 

Failures of the Resonance Picture For many years, chemists assumed that benzene's large resonance energy resulted from having two identical, stable resonance structures. They thought that other hydrocarbons with analogous conjugated systems of alternating single and double bonds would show similar stability. These cyclic hydrocarbons with alternating single and double bonds are called **annulenes**. For example, benzene is the six-membered annulene, so it can be named [6]annulene. Cyclobutadiene is [4]annulene, cyclooctatetraene is [8]annulene, and larger annulenes are named similarly.

cyclobutadiene	benzene	cyclooctatetraene	cyclodecapentaene
[4]annulene	[6]annulene	[8]annulene	[10]annulene

For the double bonds to be completely conjugated, the annulene must be planar so the *p* orbitals of the pi bonds can overlap. As long as an annulene is assumed to be planar, we can draw two Kekulé-like structures that seem to show a benzene-like resonance. Figure 17-3 shows proposed benzene-like resonance forms for cyclobutadiene and cyclooctatetraene. Although these resonance structures imply that the [4] and [8]annulenes should be unusually stable (like benzene), experiments have shown that cyclobutadiene and cyclooctatetraene are not unusually stable. These results imply that the simple resonance picture is incorrect.

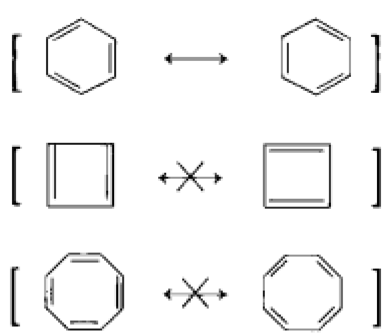
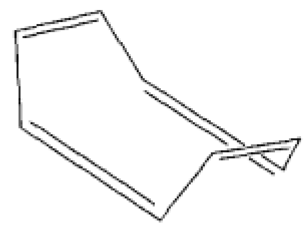


Figure 17-3 Cyclobutadiene and cyclooctatetraene have alternating single and double bonds similar to those of benzene.

Cyclobutadiene has never been isolated and purified. It undergoes an extremely fast Diels-Alder dimerization. To avoid the Diels-Alder reaction, cyclobutadiene has been prepared at low concentrations in the gas phase and as individual molecules trapped in frozen argon at low temperatures. This is not the behavior we expect from a molecule with exceptional stability!

In 1911, Richard Willstätter synthesized cyclooctatetraene and found that it reacts like a normal polyene. Bromine adds readily to cyclooctatetraene, and permanganate oxidizes its double bonds. This evidence shows that cyclooctatetraene is much less stable than benzene. In fact, structural studies have shown that cyclooctatetraene is not planar. It is most stable in a "tub" conformation, with poor overlap between adjacent pi bonds.



"tub" conformation of cyclooctatetraene

Visualizing benzene as a resonance hybrid of two Kekulé structures cannot fully explain the unusual stability of the aromatic ring. As we have seen with other conjugated systems, molecular orbital theory provides the key to understanding aromaticity and predicting which compounds will have the stability of an aromatic system.

PROBLEM 17−3

(**a**) Draw the resonance structures of benzene, cyclobutadiene, and cyclooctatetraene, showing all the carbon and hydrogen atoms.

(**b**) Assuming that these molecules are all planar, show how the *p* orbitals on the sp^2-hybrid carbon atoms form continuous rings of overlapping orbitals above and below the plane of the carbon atoms.

17−3 The Molecular Orbitals of Benzene

Benzene has a planar ring of six sp^2-hybrid carbon atoms, each with an unhybridized *p* orbital that overlaps with the *p* orbitals of its neighbors to form a continuous ring of orbitals above and below the plane of the carbon atoms. Six pi electrons are contained in this ring of overlapping *p* orbitals.

The six overlapping *p* orbitals create a cyclic system of molecular orbitals. Cyclic systems of molecular orbitals differ from linear systems such as 1,3-butadiene and the allyl system. A two-dimensional cyclic system requires two-dimensional MOs, with the possibility of two distinct MOs having the same energy. We can still follow the same principles in developing a molecular orbital representation for benzene, however.

1. There are six atomic *p* orbitals that overlap to form the benzene pi system. Therefore, there must be six molecular orbitals.

2. The lowest-energy molecular orbital is entirely bonding, with constructive overlap between all pairs of adjacent *p* orbitals. There are no vertical nodes in this lowest-lying MO.

3. The number of nodes increases as the MOs increase in energy.

4. The MOs should be evenly divided between bonding and antibonding MOs, with the possibility of nonbonding MOs in some cases.

5. We expect that a stable system will have filled bonding MOs and empty antibonding MOs.

Figure 17−4 shows the six π molecular orbitals of benzene as viewed from above, showing the sign of the top lobe of each *p* orbital. The first MO (π_1) is entirely bonding, with no nodes. It is very low in energy be-

cause it has six bonding interactions and the electrons are delocalized over all six carbon atoms. The top lobes of the *p* orbitals all have the same sign, as do the bottom lobes. The six *p* orbitals overlap to form a continuously bonding ring of electron density.

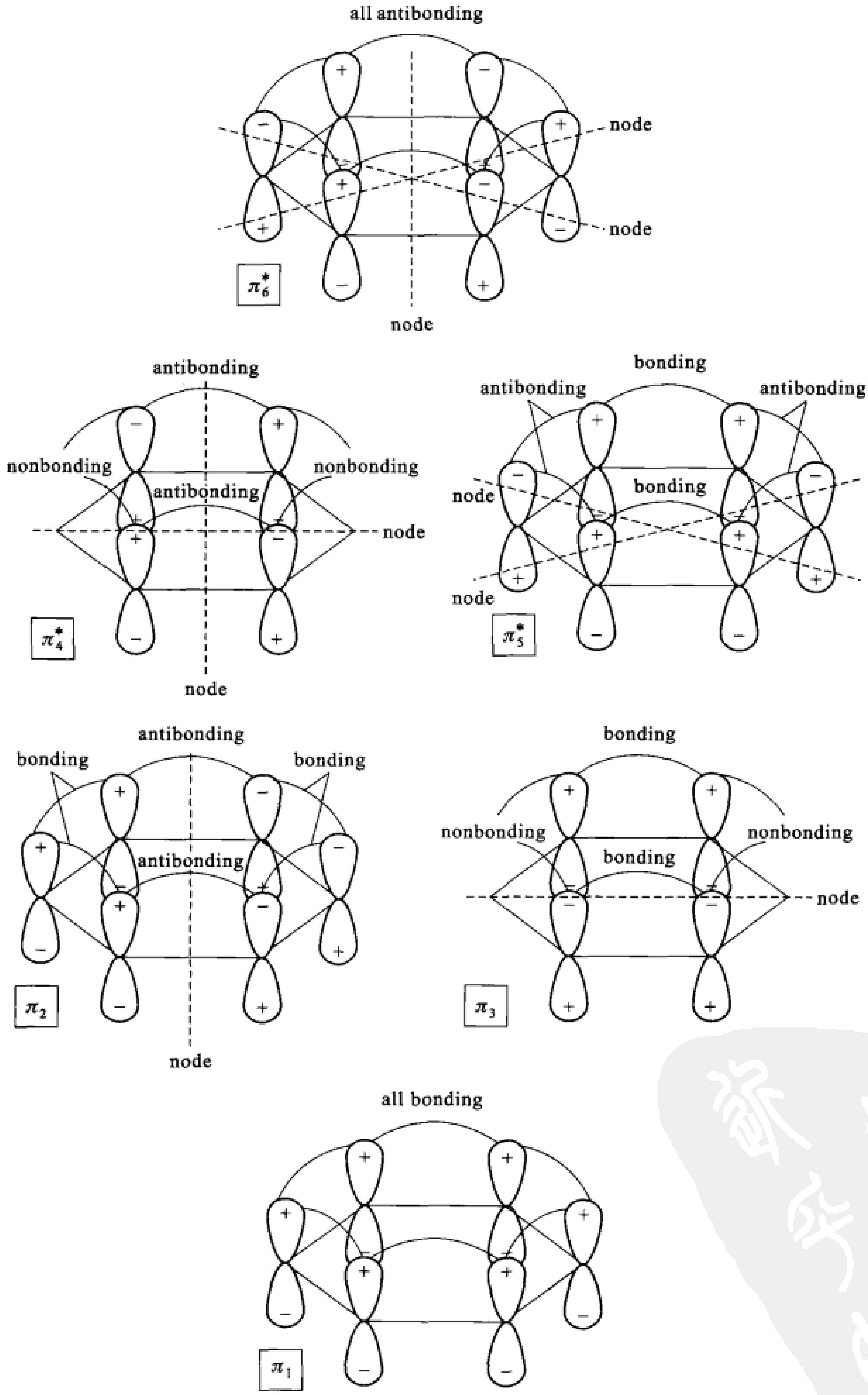


Figure 17−4 The six π molecular orbitals of benzene.

In a cyclic system of overlapping p orbitals, the intermediate energy levels are **degenerate** (equal in energy), with two orbitals at each energy level. Both π_2 and π_3 have one nodal plane, as we expect at the second energy level. Notice that π_2 has four bonding interactions and two antibonding interactions, for a total of two net bonding interactions. Similarly, π_3 has two bonding interactions and four nonbonding interactions, also totaling two net bonding interactions. Although we cannot use the number of bonding and antibonding interactions as a quantitative measure of an orbital's energy, it is clear that π_2 and π_3 are bonding MOs, but not as strongly bonding as π_1.

The π_4^* and π_5^* are also degenerate, with two nodal planes in each. The π_4^* orbital has two antibonding interactions and four nonbonding interactions; it is an antibonding (*) orbital. Its degenerate partner, π_5^*, has four antibonding interactions and two bonding interactions, for a total of two antibonding interactions. This degenerate pair of MOs, π_4^* and π_5^*, are about as strongly antibonding as π_2 and π_3 are bonding.

The all-antibonding π_6^* has three nodal planes. Each pair of adjacent p orbitals is out of phase and interacts destructively.

The Energy Diagram of Benzene The energy diagram of the benzene MOs (Figure 17-5) shows them to be symmetrically distributed above and below the nonbonding line (the energy of an isolated p orbital). The all-bonding and all-antibonding orbitals (π_1 and π_6^*) are lowest and highest in energy, respectively. The degenerate bonding orbitals (π_2 and π_3) are higher in energy than π_1, but still bonding. The degenerate pair π_4^* and π_5^* are antibonding, yet not as high in energy as the all-antibonding π_6^* orbital.

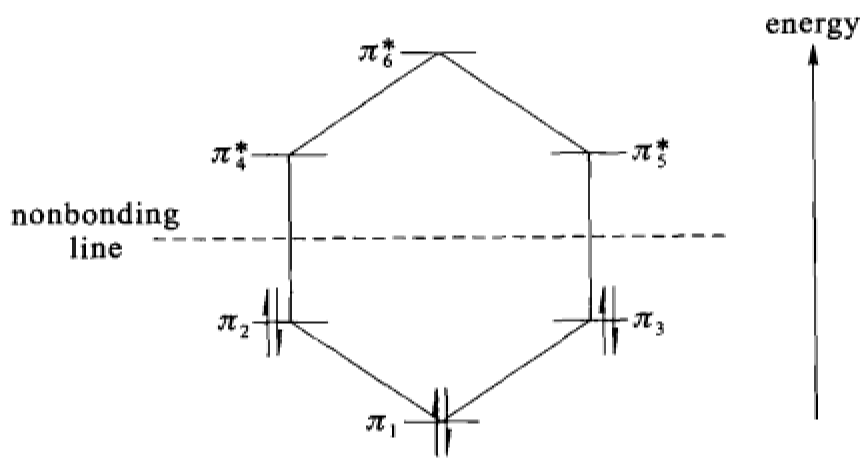


Figure 17-5 Energy diagram of the molecular orbitals of benzene.

The Kekulé structure for benzene shows three pi bonds, representing six electrons (three pairs) involved in pi bonding. Six electrons fill the three bonding MOs of the benzene system. This electronic configuration explains the unusual stability of benzene. The first MO is all-bonding and is particularly stable. The second and third (degenerate) MOs are still strongly bonding, and all three of these bonding MOs delocalize the electrons over several nuclei. This configuration, with all the bonding MOs filled (a "closed bonding shell"), is energetically very favorable.

17-4 Aromatic, Antiaromatic, and Nonaromatic Compounds

Our working definition of aromatic compounds has included cyclic compounds containing conjugated double bonds with unusually large resonance energies. At this point we can be more specific about the properties that are required for a compound (or an ion) to be aromatic.

Aromatic compounds are those that meet the following criteria:

1. The structure must be cyclic, containing some number of conjugated pi bonds.

2. Each atom in the ring must have an unhybridized *p* orbital. (The ring atoms are usually sp^2 hybridized or occasionally *sp* hybridized.)

3. The unhybridized *p* orbitals must overlap to form a continuous ring of parallel orbitals. In most cases, the structure must be planar (or nearly planar) for effective overlap to occur.

4. Delocalization of the pi electrons over the ring must *lower* the electronic energy.

An **antiaromatic compound** is one that meets the first three criteria, but delocalization of the pi electrons over the ring *increases* the electronic energy.

Aromatic structures are more stable than their open-chain counterparts. For example, benzene is more stable than 1,3,5-hexatriene.

Cyclobutadiene meets the first three criteria for a continuous ring of overlapping *p* orbitals, but delocalization of the pi electrons *increases* the electronic energy. Cyclobutadiene is less stable than its open-chain counterpart (1,3-butadiene), and it is antiaromatic.

more stable (aromatic)　　less stable　　less stable (antiaromatic)　　more stable

A cyclic compound that does not have a continuous, overlapping ring of *p* orbitals cannot be aromatic or antiaromatic. It is said to be **nonaromatic**, or aliphatic. Its electronic energy is similar to that of its open-chain counterpart. For example, 1,3-cyclohexadiene is about as stable as *cis*, *cis*-2,4-hexadiene.

(nonaromatic)

17−5 Hückel's Rule

Erich Hückel developed a shortcut for predicting which of the annulenes and related compounds are aromatic and which are antiaromatic. In using Hückel's rule, we must be certain that the compound under consideration meets the criteria for an aromatic or antiaromatic system.

To qualify as aromatic or antiaromatic, a cyclic compound must have a continuous ring of overlapping *p* orbitals, usually in a planar conformation.

Once these criteria are met, **Hückel's rule** applies:

Hückel's Rule: If the number of pi electrons in the cyclic system is:

$(4N+2)$, the system is aromatic;

$(4N)$, the system is antiaromatic,

where N is an integer.

Common aromatic systems have 2, 6, or 10 pi electrons, for $N = 0, 1$, or 2.

Antiaromatic systems might have 4, 8, or 12 pi electrons, for $N = 1, 2$, or 3.

Benzene is [6]annulene, cyclic, with a continuous ring of overlapping *p* orbitals. There are six pi electrons in benzene (three double bonds in the classical structure), so it is a $(4N+2)$ system, with $N = 1$. Hückel's rule predicts benzene to be aromatic.

Like benzene, cyclobutadiene ([4]annulene) has a continuous ring of overlapping *p* orbitals, but it has

four pi electrons (two double bonds in the classical structure). Hückel's rule predicts cyclobutadiene to be antiaromatic.

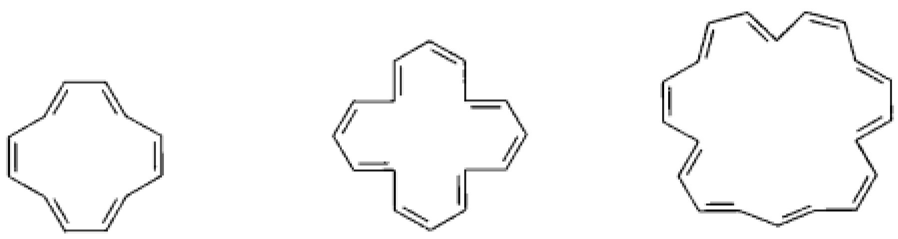
Cyclooctatetraene is [8]annulene, with eight pi electrons (four double bonds) in the classical structure. It is a $4N$ system, with $N=2$. If Hückel's rule were applied to cyclooctatetraene, it would predict antiaromaticity. However, cyclooctatetraene is a stable hydrocarbon with a boiling point of 153 ℃. It does not show the high reactivity associated with antiaromaticity, yet it is not aromatic either. Its reactions are typical of alkenes.

Cyclooctatetraene would be antiaromatic if Hückel's rule applied, so the conjugation of its double bonds is energetically unfavorable. Remember that Hückel's rule applies to a compound *only* if there is a continuous ring of overlapping *p* orbitals, usually in a planar system. Cyclooctatetraene is more flexible than cyclobutadiene, and it assumes a nonplanar "tub" conformation that avoids most of the overlap between adjacent pi bonds. Hückel's rule simply does not apply.

PROBLEM 17-4

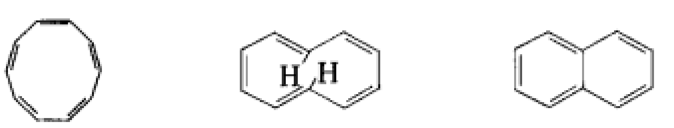
Make a model of cyclooctatetraene in the tub conformation. Draw this conformation, and estimate the angle between the *p* orbitals of adjacent pi bonds.

Large-Ring Annulenes Like cyclooctatetraene, larger annulenes with $4N$ systems do not show antiaromaticity because they have the flexibility to adopt nonplanar conformations. Even though [12]annulene, [16]annulene, and [20]annulene are $4N$ systems (with $N=3, 4$, and 5, respectively), they all react as partially conjugated polyenes.



[12]annulene ([12]轮烯) [16]annulene [20]annulene

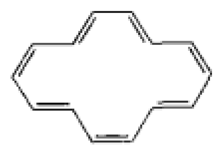
Aromaticity in the larger $4N+2$ annulenes depends on whether the molecule can adopt the necessary planar conformation. In the all-cis [10]annulene, the planar conformation requires an excessive amount of angle strain. The [10]annulene isomer with two trans double bonds cannot adopt a planar conformation either, because two hydrogen atoms interfere with each other. Neither of these [10]annulene isomers is aromatic. even though each has $(4N+2)$ pi electrons, with $N=2$. If the interfering hydrogen atoms in the partially trans isomer are removed, the molecule can be planar. When these hydrogen atoms are replaced with a bond, the aromatic compound naphthalene results.

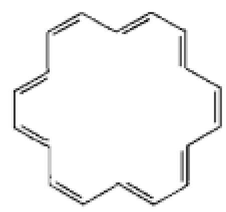


all-cis nonaromatic two trans nonaromatic naphthalene aromatic

Some of the larger annulenes with $(4N+2)$ pi electrons can achieve planar conformations. For example, the fol-

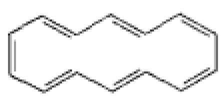
lowing [14]annulene and [18]annulene have aromatic properties.


[14]annulene (aromatic)

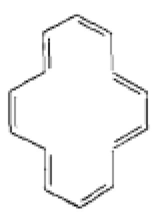

[18]annulene (aromatic)

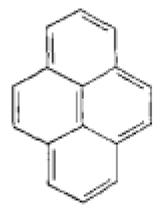
PROBLEM 17-5

Classify the following compounds as aromatic, antiaromatic, or nonaromatic.

(a) 

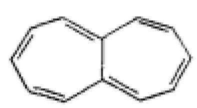
(b)

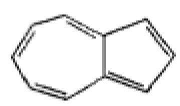
(c) 

(d) 

PROBLEM 17-6

One of the following compounds is much more stable than the other two. Classify each as aromatic, antiaromatic, or nonaromatic.


heptalene
（庚搭烯，并环庚三烯）


azulene
（薁）

pentalene
（并环戊二烯）

17-6 Molecular Orbital Derivation of Hückel's Rule

Benzene is aromatic because it has a filled shell of equal-energy orbitals. The degenerate orbitals π_2 and π_3 are filled, and all the electrons are paired. Cyclobutadiene, by contrast, has an open shell of electrons. There are two half-filled orbitals easily capable of donating or accepting electrons. To derive Hückel's rule, we must show under what general conditions there is a filled shell of orbitals.

Recall the pattern of MOs in a cyclic conjugated system. There is one all-bonding, lowest-lying MO, followed by degenerate pairs of bonding MOs. (There is no need to worry about the antibonding MOs because they are vacant in the ground state.) The lowest-lying MO is always filled (two electrons). Each additional shell consists of two degenerate MOs, requiring four electrons to fill a shell. Figure 17-6 shows this pattern of two electrons for the lowest orbital and then four electrons for each additional shell.

A compound has a filled shell of orbitals if it has two electrons for the lowest-lying orbital, plus $4N$ electrons, where N is the number of filled pairs of degenerate orbitals. The total number of pi electrons in this case is $(4N+2)$. If the system has a total of only $4N$ electrons, it is two electrons short of filling N pairs of degener-

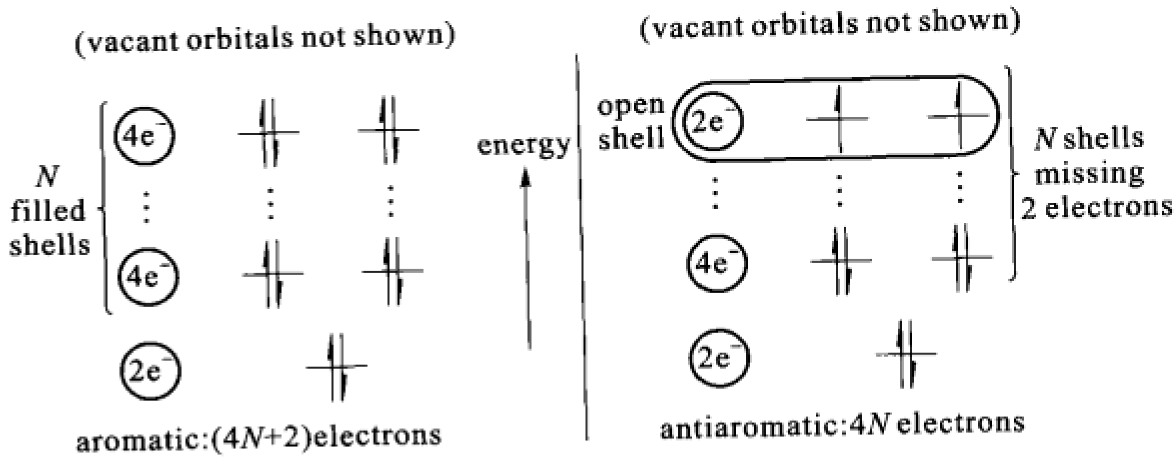


Figure 17-6 Pattern of molecular orbitals in a cyclic conjugated system.

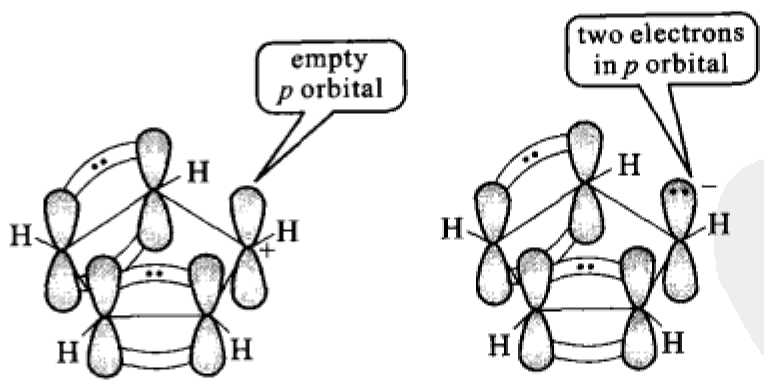
ate orbitals. There are only two electrons in the Nth pair of degenerate orbitals. This is a half-filled shell, and Hückel's rule predicts these electrons will be unpaired (a diradical).

17-7 Aromatic Ions

Up to this point, we have discussed aromaticity using the annulenes as examples. Annulenes are uncharged molecules having even numbers of carbon atoms with alternating single and double bonds. Hückel's rule also applies to systems having odd numbers of carbon atoms and bearing positive or negative charges. We now consider some common aromatic ions and their antiaromatic counterparts.

17-7A The Cyclopentadienyl Ions

We can draw a five-membered ring of sp^2-hybrid carbon atoms with all the unhybridized p orbitals lined up to form a continuous ring. With five pi electrons, this system would be neutral, but it would be a radical because an odd number of electrons cannot all be paired. With four pi electrons (a cation), Hückel's rule predicts this system to be antiaromatic. With six pi electrons (an anion), Hückel's rule predicts aromaticity.

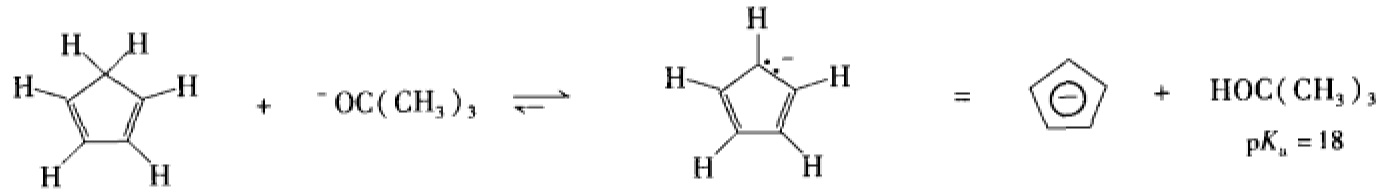


four electrons
cyclopentadienyl cation
（环戊二烯正离子）

six electrons
cyclopentadienyl anion
（环戊二烯负离子）

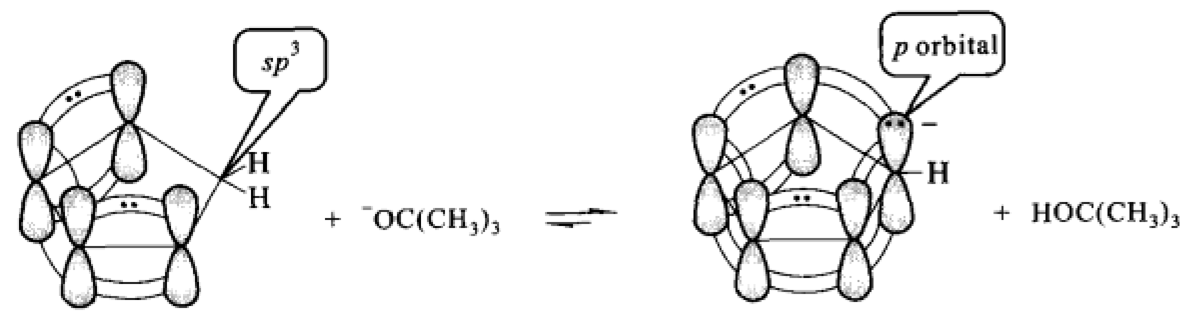
Because the cyclopentadienyl anion (six pi electrons) is aromatic, it is unusually stable compared with other carbanions. It can be formed by abstracting a proton from cyclopentadiene, which is unusually acidic for an alkene. Cyclopentadiene has a pK_a of 16, compared with a pK_a of 46 for cyclohexene. In fact, cyclopentadiene is nearly as acidic as water and more acidic than many alcohols. It is entirely ionized by potassium t-bu-

toxide:



$pK_a = 16$ — the cyclopentadienyl anion (six pi electrons) — $pK_a = 18$

Cyclopentadiene is unusually acidic because loss of a proton converts the nonaromatic diene to the aromatic cyclopentadienyl anion. Cyclopentadiene contains an sp^3-hybrid ($—CH_2—$) carbon atom without an unhybridized p orbital, so there can be no continuous ring of p orbitals. Deprotonation of the $—CH_2—$ group leaves an orbital occupied by a pair of electrons. This orbital can rehybridize to a p orbital, completing a ring of p orbitals containing six pi electrons: the two electrons on the deprotonated carbon, plus the four electrons in the original double bonds.

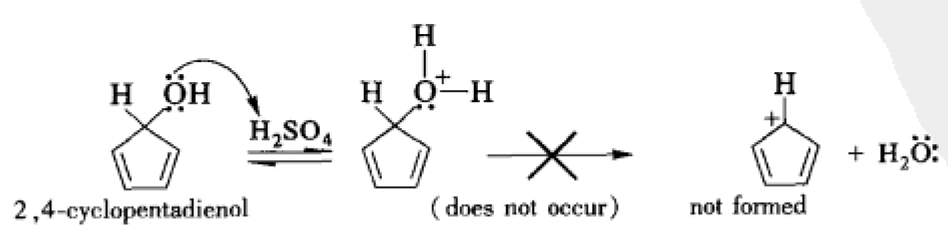


cyclopentadiene (环戊二烯) nonaromatic — cyclopentadienyl anion (环戊二烯负离子) aromatic

When we say the cyclopentadienyl anion is aromatic, this does not necessarily imply that it is as stable as benzene. As a carbanion, the cyclopentadienyl anion reacts readily with electrophiles. Because this ion is aromatic, it is more stable than the corresponding open-chain ion.

more stable (aromatic) — less stable

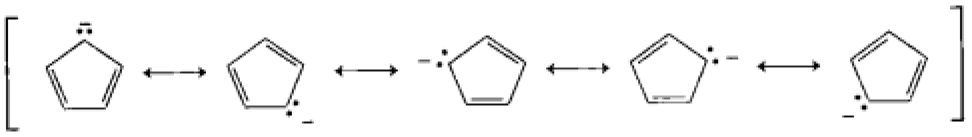
Hückel's rule predicts that the cyclopentadienyl cation, with four pi electrons, is antiaromatic. In agreement with this prediction, the cyclopentadienyl cation is not easily formed. Protonated 2,4-cyclopentadienol does not lose water (to give the cyclopentadienyl cation), even in concentrated sulfuric acid. The antiaromatic cation is simply too unstable.



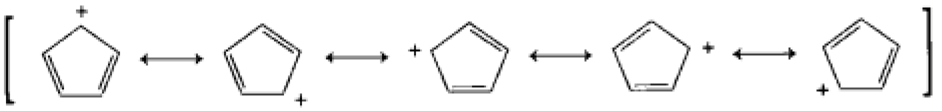
2,4-cyclopentadienol — (does not occur) — not formed (four pi electrons)

Using a simple resonance approach, we might incorrectly expect both of the cyclopentadienyl ions to be unusually stable. Shown next are resonance structures that spread the negative charge of the anion and the positive charge of the cation over all five carbon atoms of the ring. With conjugated cyclic systems such as these, the res-

onance approach is a poor predictor of stability. The Hückel's rule, based on molecular orbital theory, is a much better predictor of stability for these aromatic and antiaromatic systems.



cyclopentadienyl anion: six pi electrons, aromatic

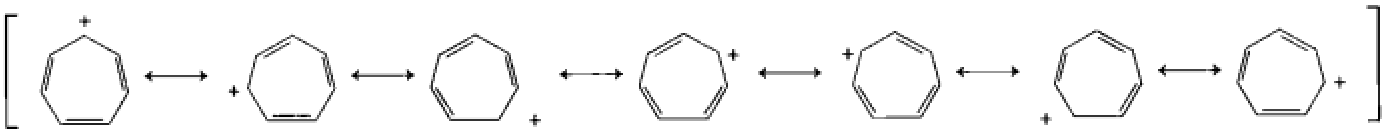


cyclopentadienyl cation: four pi electrons, antiaromatic

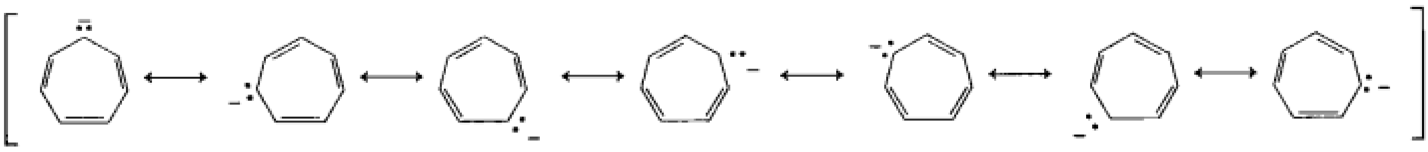
The resonance picture gives a misleading suggestion of stability.

17–7B The Cycloheptatrienyl Ions

As with the five-membered ring, we can imagine a flat seven-membered ring with seven *p* orbitals aligned. The cation has six pi electrons, and the anion has eight pi electrons. Once again, we can draw resonance forms that seem to show either the positive charge of the cation or the negative charge of the anion delocalized over all seven atoms of the ring. By now, however, we know that the six-electron system is aromatic and the eight-electron system is antiaromatic (if it remains planar).



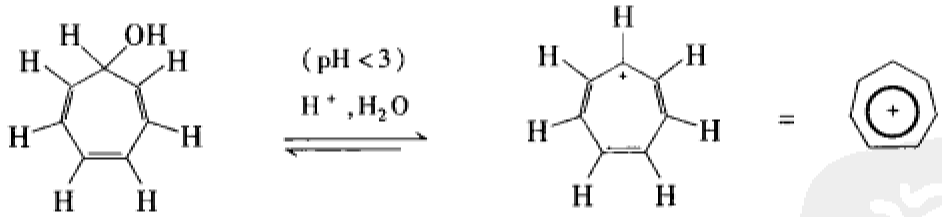
cycloheptatrienyl cation (tropylium ion): six pi electrons, aromatic



cycloheptatrienyl anion: eight pi electrons, antiaromatic (if planar)

The resonance picture gives a misleading suggestion of stability.

The cycloheptatrienyl cation is easily formed by treating the corresponding alcohol with dilute aqueous sulfuric acid. This is our first example of a hydrocarbon cation that is stable in aqueous solution.



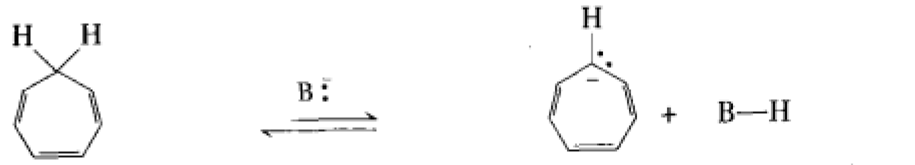
tropylium ion, six pi electrons

The cycloheptatrienyl cation is called the **tropylium ion**. This aromatic ion is much less reactive than most carbocations. Some tropylium salts can be isolated and stored for months without decomposing. Nevertheless, the tropylium ion is not necessarily as stable as benzene. Its aromaticity implies that the cyclic ion is more stable than the corresponding open-chain ion.

more stable (aromatic) less stable

Although the tropylium ion forms easily, the corresponding anion is difficult to form because it is antiaromat-

ic. Cycloheptatriene ($pK_a = 39$) is barely more acidic than propene ($pK_a = 43$), and the anion is very reactive. This result agrees with the prediction of Hückel's rule that the cycloheptatrienyl anion is antiaromatic.

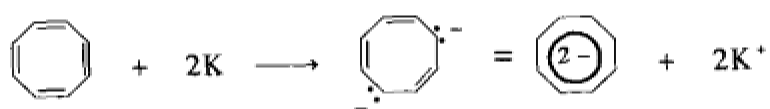


cycloheptatriene(环庚三烯) $pK_a = 39$

cycloheptatrienyl anion(环庚三烯负离子) eight pi electrons

17-7C The Cyclooctatetraene Dianion

We have seen that aromatic stabilization leads to unusually stable hydrocarbon anions such as the cyclopentadienyl anion. Dianions of hydrocarbons are rare and are usually much more difficult to form. Cyclooctatetraene reacts with potassium metal, however, to form an aromatic dianion.

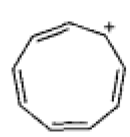


ten pi electrons

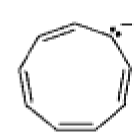
The cyclooctatetraene dianion has a planar, regular octagonal structure with C—C bond lengths of 1.40 Å, close to the 1.397 Å bond lengths in benzene. Cyclooctatetraene itself has eight pi electrons, so the dianion has ten: $(4N+2)$, with $N=2$. The cyclooctatetraene dianion is easily prepared because it is aromatic.

PROBLEM 17-7

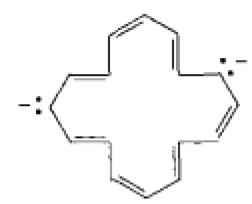
Explain why each compound or ion should be aromatic, antiaromatic, or nonaromatic.

(a) 

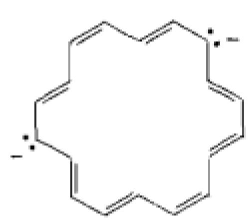
the cyclononatetraene cation

(b) 

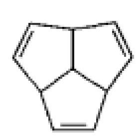
the cyclononatetraene anion

(c) 

the [16]annulene dianion

(d) 

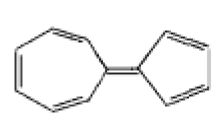
the [18]annulene dianion

(e) 

(f) the [20]annulene dication

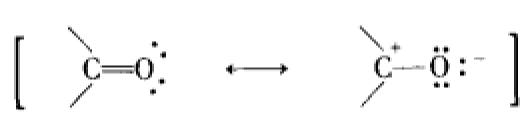
PROBLEM 17-8

The following hydrocarbon has an unusually large dipole moment. Explain how a large dipole moment might arise.

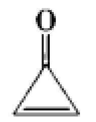


PROBLEM 17-9

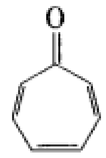
The polarization of a carbonyl group can be represented by a pair of resonance structures:



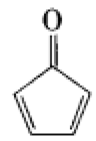
Cyclopropenone and cycloheptatrienone are more stable than anticipated. Cyclopentadienone, however, is relatively unstable and rapidly undergoes a Diels-Alder dimerization. Explain.



cyclopropenone
(环丙烯酮)



cycloheptatrienone
(环庚三烯酮)



cyclopentadienone
(环戊二烯酮)

17-8 Heterocyclic Aromatic Compounds

The criteria for Hückel's rule require a ring of atoms, all with unhybridized *p* orbitals overlapping in a continuous ring. In discussing aromaticity, we have considered only compounds composed of rings of sp^2-hybrid carbon atoms. **Heterocyclic compounds**, with rings containing sp^2-hybridized atoms of other elements, can also be aromatic. Nitrogen, oxygen, and sulfur are the most common heteroatoms in heterocyclic aromatic compounds.

17-8A Pyridine

Pyridine is an aromatic nitrogen analogue of benzene. It has a six-membered heterocyclic ring with six pi electrons. Pyridine has a nitrogen atom in place of one of the six C—H units of benzene, and the nonbonding pair of electrons on nitrogen replaces the bond to a hydrogen atom. These nonbonding electrons are in an sp^2-hybrid orbital in the plane of the ring (Figure 17-7). They are perpendicular to the pi system and do not overlap with it.

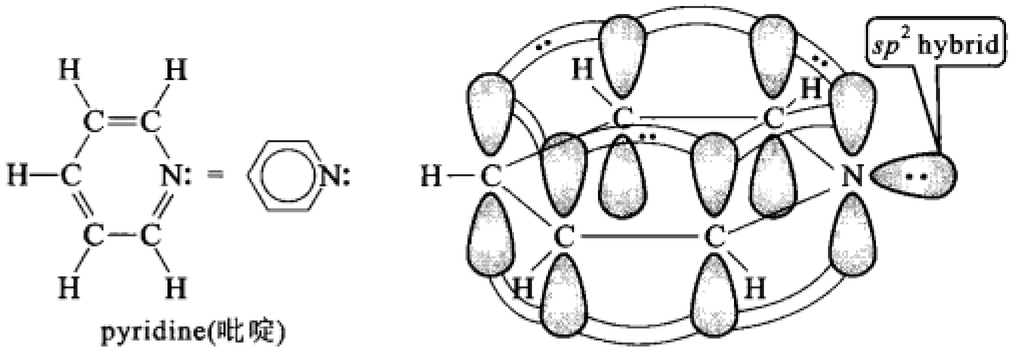


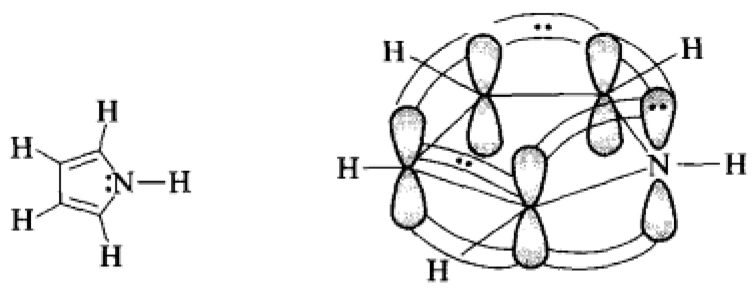
Figure 17-7 The pi bonding structure of pyridine.

Pyridine shows all the characteristics of aromatic compounds. It has a resonance energy of 113 kJ/mol and it usually undergoes substitution rather than addition. Because it has an available pair of nonbonding electrons, pyridine is basic. In an acidic solution, pyridine protonates to give the pyridinium ion. The pyridinium ion is still aromatic because the additional proton has no effect on the electrons of the aromatic sextet: It simply bonds to pyridine's nonbonding pair of electrons.

pyridine, $pK_b = 8.8$ pyridinium ion, $pK_a = 5.2$
(吡啶鎓离子)

17-8B Pyrrole

Pyrrole is an aromatic five-membered heterocycle, with one nitrogen atom and two double bonds (Figure 17-8). Although it may seem that pyrrole has only four pi electrons, the nitrogen atom has a lone pair of electrons. The pyrrole nitrogen atom is sp^2 hybridized, and its unhybridized p orbital overlaps with the p orbitals of the carbon atoms to form a continuous ring. The lone pair on nitrogen occupies the p orbital, and (unlike the lone pair of pyridine) these electrons take part in the pi bonding system. These two electrons, added to the four pi electrons of the two double bonds, complete an aromatic sextet. Pyrrole has a resonance energy of 92 kJ/mol.

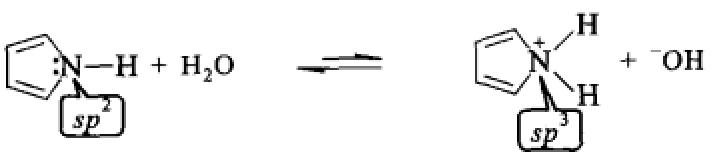


pyrrole

orbital structure of pyrrole (six pi electrons, aromatic)

Figure 17-8 The pi bonding structure of pyrrole.

Pyrrole ($pK_b = 13.6$) is a much weaker base than pyridine ($pK_b = 8.8$). This difference is due to the structure of the protonated pyrrole. To form a bond to a proton requires the use of one of the electron pairs in the aromatic sextet. In the protonated pyrrole, the nitrogen atom is bonded to four different atoms (two carbon atoms and two hydrogen atoms), requiring sp^3 hybridization and leaving no unhybridized p orbital. The protonated pyrrole is nonaromatic. In fact, a sufficiently strong acid actually protonates pyrrole at the 2-position, on one of the carbon atoms of the ring, rather than on nitrogen.



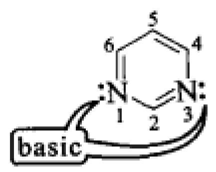
pyrrole, $pK_b = 13.6$ (weak base) (吡咯)

N-protonated pyrrole, $pK_a = 0.4$ (strong acid) (N-质子化的吡咯)

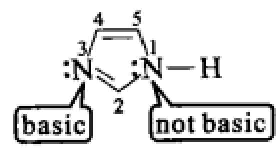
17-8C Pyrimidine and Imidazole

Pyrimidine is a six-membered heterocycle with two nitrogen atoms situated in a 1,3 arrangement. Both nitrogen atoms are like the pyridine nitrogen. Each has its lone pair of electrons in the sp^2-hybrid orbital in the plane of the aromatic ring. These lone pairs are not needed for the aromatic sextet, and they are basic, like the lone pair of pyridine.

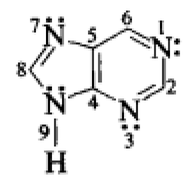
Imidazole is an aromatic five-membered heterocycle with two nitrogen atoms. The lone pair of one of the nitrogen atoms (the one not bonded to a hydrogen) is in an sp^2 orbital that is not involved in the aromatic system; this lone pair is basic. The other nitrogen uses its third sp^2 orbital to bond to hydrogen, and its lone pair is part of the aromatic sextet. Like the pyrrole nitrogen atom, this imidazole N—H nitrogen is not very basic. Once im-



pyrimidine
(嘧啶)

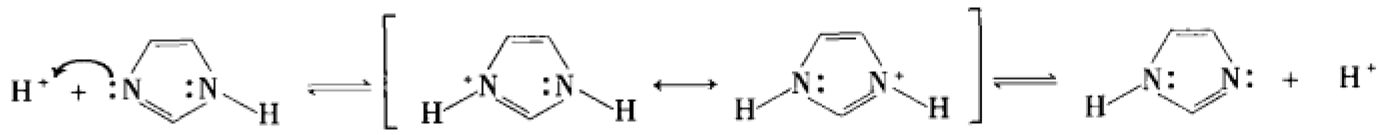


imidazole
(咪唑)



purine
(嘌呤)

idazole is protonated, the two nitrogens become chemically equivalent. Either nitrogen can lose a proton and return to an imidazole molecule.



imidazole   protonated imidazole   imidazole

Purine has an imidazole ring fused to a pyrimidine ring. Purine has three basic nitrogen atoms and one pyrrole-like nitrogen.

Pyrimidine and purine derivatives serve in DNA and RNA to specify the genetic code. Imidazole derivatives enhance the catalytic activity of enzymes. We will consider these important heterocyclic derivatives in more detail in Chapters 24 and 25.

17−8D Furan and Thiophene

Furan is an aromatic five-membered heterocycle-like pyrrole, but the heteroatom is oxygen instead of nitrogen. The classical structure for furan (Figure 17−9) shows that the oxygen atom has two lone pairs of electrons. The oxygen atom is sp^2 hybridized, and one of the lone pairs occupies an sp^2-hybrid orbital. The other lone pair occupies the unhybridized p orbital, combining with the four electrons in the double bonds to give an aromatic sextet. Furan has a resonance energy of 67 kJ/mol.

Thiophene is similar to furan, with a sulfur atom in place of the furan oxygen. The bonding in thiophene is similar to that in furan, except that the sulfur atom uses an unhybridized $3p$ orbital to overlap with the $2p$ orbitals on the carbon atoms. The resonance energy of thiophene is 121 kJ/mol.

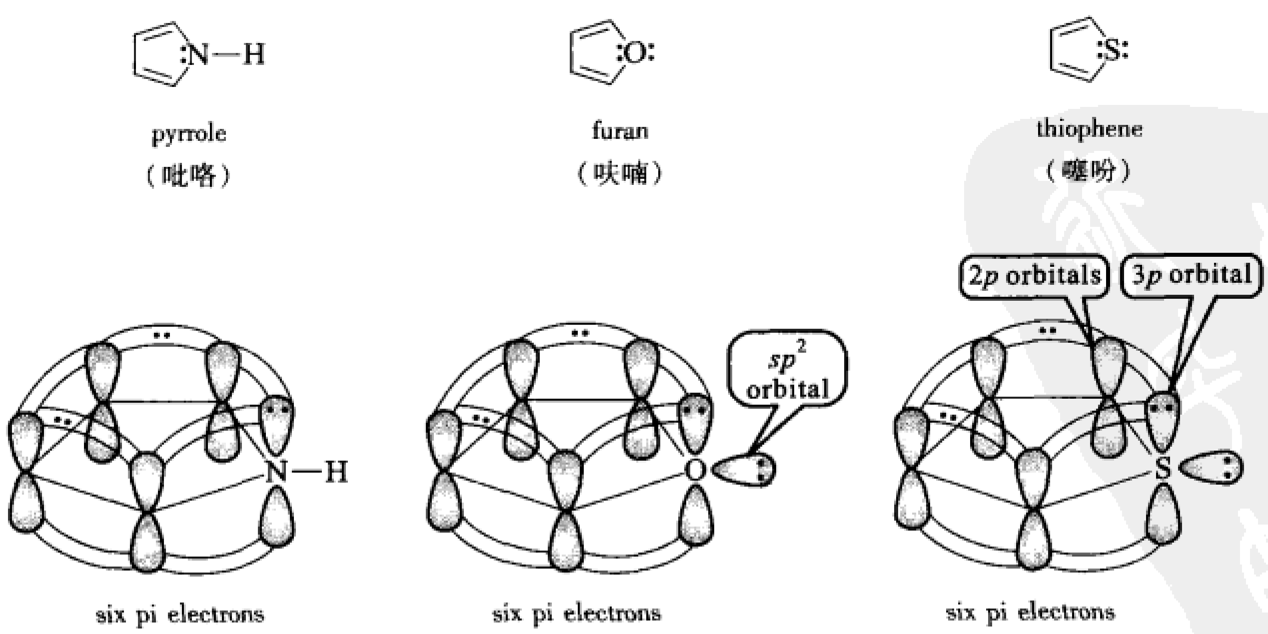
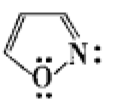


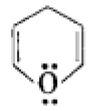
Figure 17−9 Pyrrole, furan, and thiophene are isoelectronic.

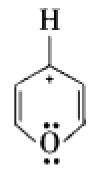
PROBLEM 17-10

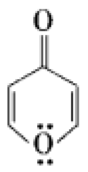
Explain why each compound is aromatic, antiaromatic, or nonaromatic.

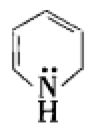
(a) 
isoxazole
(异噁唑)

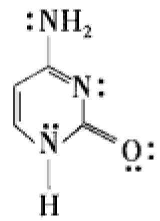
(b)
1,3-thiazole
(1,3-噻唑)

(c) 
pyran
(吡喃)

(d) 
pyrylium ion
(吡喃鎓离子)

(e) 
γ-pyrone
(γ-吡喃酮)

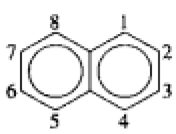
(f) 
1,2-dihydropyridine
(1,2-二氢化吡啶)

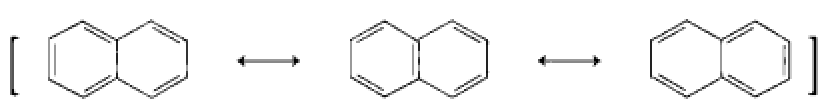
(g) 
cytosine
(胞嘧啶)

17-9 Polynuclear Aromatic Hydrocarbons

The **polynuclear aromatic hydrocarbons** (abbreviated PAHs or PNAs) are composed of two or more fused benzene rings. **Fused rings** share two carbon atoms and the bond between them.

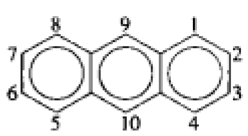
Naphthalene Naphthalene ($C_{10}H_8$) is the simplest fused aromatic compound, consisting of two fused benzene rings. We represent naphthalene by using one of the three Kekulé resonance structures or using the circle notation for the aromatic rings.

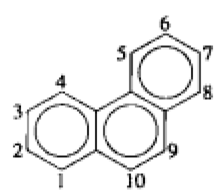

naphthalene

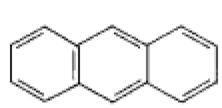


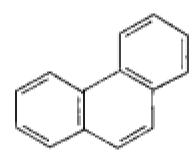
The two aromatic rings in naphthalene contain a total of 10 pi electrons. Two isolated aromatic rings would contain 6 pi electrons in each aromatic system, for a total of 12. The smaller amount of electron density gives naphthalene less than twice the resonance energy of benzene: 252 kJ/mol, or 126 kJ, per aromatic ring, compared with benzene's resonance energy of 151 kJ/mol.

Anthracene and Phenanthrene As the number of fused aromatic rings increases, the resonance energy per ring continues to decrease and the compounds become more reactive. Tricyclic anthracene has a resonance energy of 351 kJ/mol, or 117 kJ, per aromatic ring. Phenanthrene has a slightly higher resonance energy of 381 kJ/mol, or about 127 kJ, per aromatic ring. Each of these compounds has only 14 pi electrons in its three aromatic rings, compared with 18 electrons for three separate benzene rings.



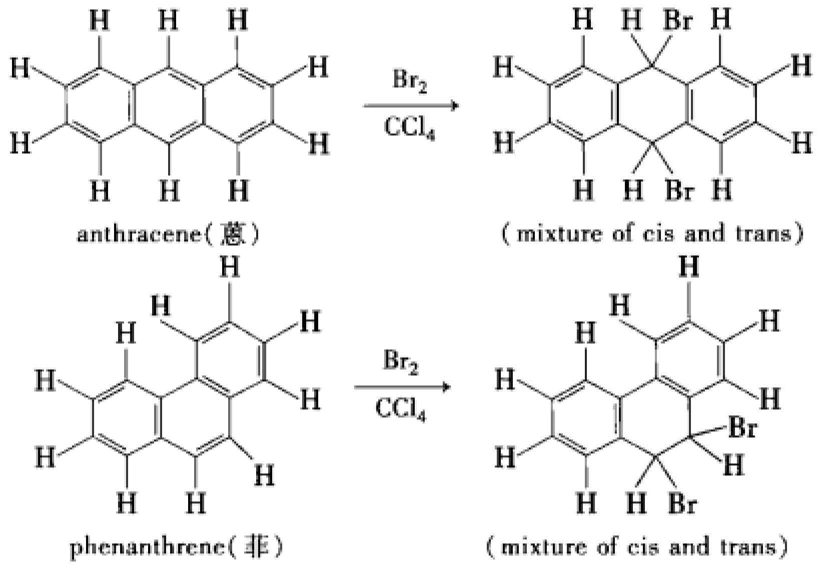



anthracene(蒽)

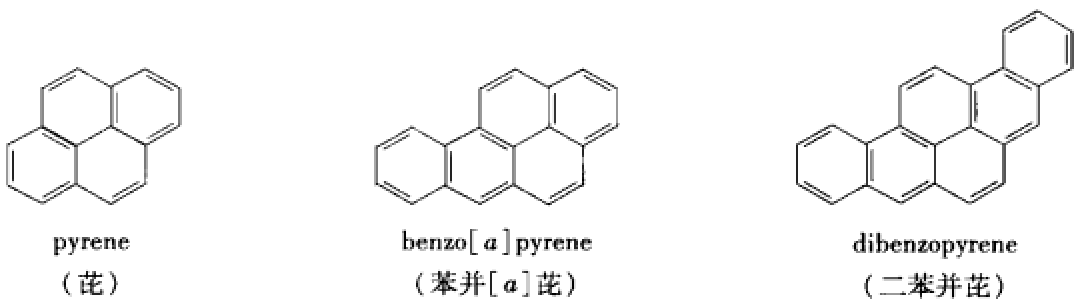

phenanthrene(菲)

(Only one Kekulé structure is shown for each compound.)

Because they are not as strongly stabilized as benzene, anthracene and phenanthrene can undergo addition reactions that are more characteristic of their nonaromatic polyene relatives. Anthracene undergoes 1,4-addition at the 9-and 10-positions to give a product with two isolated, fully aromatic benzene rings. Similarly, phenanthrene undergoes 1,2-addition at the 9- and 10-positions to give a product with two fully aromatic rings. (Because they are less likely to be substituted, the bridgehead carbon atoms of fused aromatics are often left unnumbered.)



Larger Polynuclear Aromatic Hydrocarbons There is a high level of interest in the larger PAHs because they are formed in most combustion processes and many of them are carcinogenic (capable of causing cancer). The following three compounds, for example, are present in tobacco smoke. These compounds are so hazardous that laboratories must install special containment facilities to work with them, yet smokers expose their lung tissues to them.



17−10 Aromatic Allotropes of Carbon

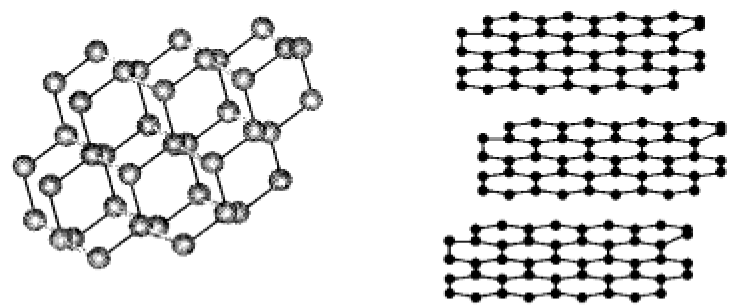
What do you get when you make an extremely large polynuclear aromatic hydrocarbon, with millions or billions of benzene rings joined together? You get graphite, one of the oldest-known forms of pure elemental carbon. Let's consider how aromaticity plays a role in the stability of both the old and the new forms of carbon.

17−10A Allotropes of Carbon: Diamond

We don't normally think of elemental carbon as an organic compound. Historically, carbon was known to exist as three allotropes (elemental forms with different properties): amorphous carbon, diamond, and graphite.

"Amorphous carbon" refers to charcoal, soot, coal, and carbon black. These materials are mostly microcrystalline forms of graphite. They are characterized by small particle sizes and large surface areas with partially saturated valences. These small particles readily absorb gases and solutes from solution, and they form strong, stable dispersions in polymers, such as the dispersion of carbon black in tires.

Diamond is the hardest naturally occurring substance known. Diamond has a crystalline structure containing tetrahedral carbon atoms linked together in a three-dimensional lattice (Figure 17−10). This lattice extends throughout each crystal, so that a diamond is actually one giant molecule. Diamond is an electrical insulator because the electrons are all tightly bound in sigma bonds (length 1.54 Å, typical of C—C single bonds), and they are unavailable to carry a current.



diamond(金刚石) graphite(石墨)

Figure 17−10 Structures of diamond and graphite.

17−10B Graphite

Graphite has the layered planar structure shown in Figure 17−10. Within a layer, the C—C bond lengths are all 1.415 Å, which is fairly close to the C—C bond length in benzene (1.397 Å). Between layers, the distance is 3.35 Å, which is about twice the van der Waals radius for carbon, suggesting there is little or no bonding between layers. The layers can easily cleave and slide across each other, making graphite a good lubricant. This layered picture also helps to explain graphite's unusual electrical properties: It is a good electrical conductor parallel to the layers, but it resists electrical currents perpendicular to the layers.

We picture each layer of graphite as a nearly infinite lattice of fused aromatic rings. All the valences are satisfied (except at the edges), and no bonds are needed between layers. Only van der Waals forces hold the layers together, consistent with their ability to slide easily over one another. The pi electrons within a layer can conduct electrical currents parallel to the layer, but electrons cannot easily jump between layers, so graphite is resistive perpendicular to the layers.

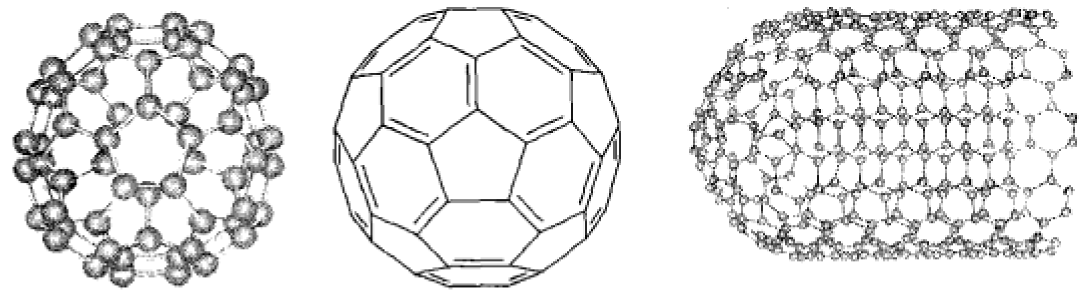
Because of its aromaticity, graphite is slightly more stable than diamond, and the transition from diamond to graphite is slightly exothermic ($\Delta H^{\ominus} = -2.9$ kJ/mol). Fortunately for those who have invested in diamonds, the favorable conversion of diamond to graphite is exceedingly slow. Diamond (3.51 g/cm^3) has a higher density than graphite (2.25 g/cm^3), implying that graphite might be converted to diamond under very high pressures. Indeed, small industrial diamonds can be synthesized by subjecting graphite to pressures over $125\,000 \times 10^5$ Pa and temperatures around 3 000 ℃, using catalysts such as Cr and Fe.

17−10C Fullerenes

Around 1985, Kroto, Smalley, and Curl (Rice University) isolated a molecule of formula C_{60} from the soot produced by using a laser (or an electric arc) to vaporize graphite. Molecular spectra showed that C_{60} is unusually symmetrical: It has only one type of carbon atom by ^{13}C NMR (δ143), and there are only two types of bonds (1.39 Å and 1.45 Å). Figure 17−11 shows the structure of C_{60}, which was named **buckminsterfullerene** in honor of the American architect R. Buckminster Fuller, whose geodesic domes used similar five- and six-membered rings to form a curved roof. The C_{60} molecules are sometimes called "buckyballs," and these types of compounds (C_{60} and similar carbon clusters) are called **fullerenes.**

A soccer ball has the same structure as C_{60}, with each vertex representing a carbon atom. All the carbon atoms are chemically the same. Each carbon serves as a bridgehead for two six-membered rings and one five-membered ring. There are only two types of bonds: the bonds that are shared by a five-membered ring and a six-membered ring (1.45 Å) and the bonds shared between two six-membered rings (1.39 Å). Compare these bond lengths with a typical double bond (1.33 Å), a typical aromatic bond (1.40 Å), and a typical single bond (1.48 Å between sp^2 carbons). It appears that the double bonds are somewhat localized between the six-mem-

bered rings, as shown in Figure 17－11. These double bonds are less reactive than typical alkene double bonds, yet they do undergo some of the addition reactions of alkenes.



buckyball (C_{60})
(足球烯)

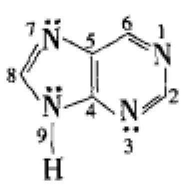
carbon nanotube
(碳纳米管)

Figure 17－11 Structure of C_{60} and a carbon nanotube.

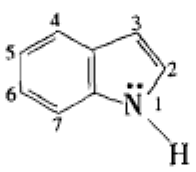
Nanotubes (Figure 17－11) were discovered around 1991. These structures begin with half of the C_{60} sphere, fused to a cylinder composed entirely of fused six-membered rings (as in a layer of graphite). Nanotubes have aroused interest because they are electrically conductive only along the length of the tube and they have an enormous strength-to-weight ratio.

17－11 Fused Heterocyclic Compounds

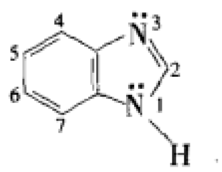
Purine is one of many fused heterocyclic compounds whose rings share two atoms and the bond between them. For example, the following compounds all contain fused heterocyclic aromatic rings:



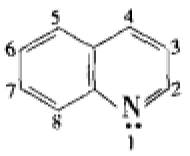
purine
(嘌呤)



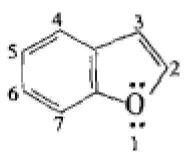
indole
(吲哚)



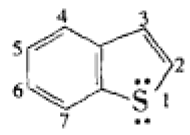
benzimidazole
(苯并咪唑)



quinoline
(喹啉)

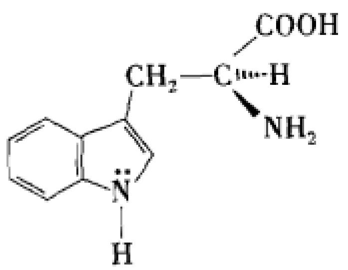


benzofuran
(苯并呋喃)

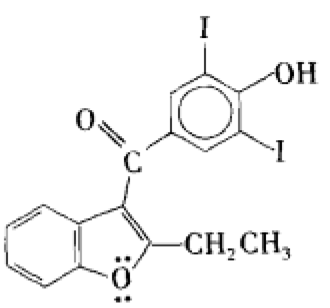


benzothiophene
(苯并噻吩)

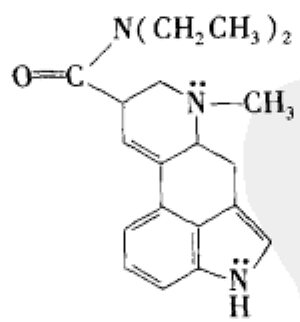
The properties of fused-ring heterocycles are generally similar to those of the simple heterocycles. Fused heterocyclic compounds are common in nature, and they are also used as drugs to treat a wide variety of illnesses. Figure 17－12 shows some fused heterocycles that occur naturally or are synthesized for use as drugs.



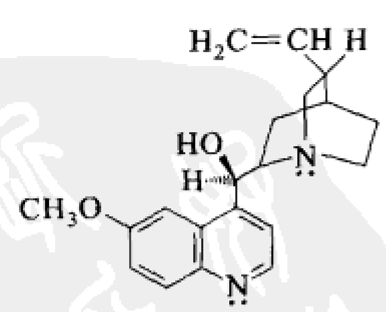
L-tryptophan, an amino acid
(色氨酸)



benziodarone, a vasodilator
(苯碘达隆，血管扩张剂)



LSD, a hallucinogen
[致幻剂(药)]



quinine, an antimalarial drug
(喹宁)

Figure 17－12 Examples of biologically active fused heterocycles.

17－12 Physical Properties of Benzene and Its Derivatives

The melting points, boiling points, and densities of benzene and some derivatives are given in Table 17－1. Ben-

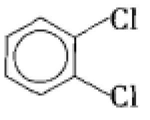
zene derivatives tend to be more symmetrical than similar aliphatic compounds, so they pack better into crystals and have higher melting points. For example, benzene melts at 6 ℃, while hexane melts at −95 ℃. Similarly, paradisubstituted benzenes are more symmetrical than the ortho and meta isomers, and they pack better into crystals and have higher melting points.

TABLE 17-1 Physical Properties of Benzene and Its Derivatives

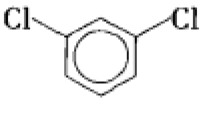
Compound	mp/℃	bp/℃	Density/($g\cdot mL^{-1}$)
benzene	6	80	0.88
toluene(甲苯)	−95	111	0.87
ethylbenzene	−95	136	0.87
styrene(苯乙烯)	−31	146	0.91
ethynylbenzene(苯乙炔)	−45	142	0.93
fluorobenzene	−41	85	1.02
chlorobenzene	−46	132	1.11
bromobenzene	−31	156	1.49
iodobenzene	−31	188	1.83
benzyl bromide(苄基溴)	−4	199	1.44
nitrobenzene	6	211	1.20
phenol(苯酚)	43	182	1.07
anisole(苯甲醚,茴香醚)	37	156	0.98
benzoic acid(苯甲酸)	122	249	1.31
benzyl alcohol(苄醇)	−15	205	1.04
aniline(苯胺)	−6	186	1.02
diphenyl ether	28	259	1.08
mesitylene(间三甲苯)	−45	165	0.87
o-xylene(邻二甲苯)	−26	144	0.88
m-xylene	−48	139	0.86
p-xylene	13	138	0.86
o-chlorotoluene(邻氯甲苯)	−35	159	1.08
m-chlorotoluene	−48	162	1.07
p-chlorotoluene	8	162	1.07
o-dichlorobenzene	−17	181	1.31
m-dichlorobenzene	−25	173	1.29
p-dichlorobenzene	54	170	1.46
o-dibromobenzene	7	225	1.62
m-dibromobenzene	−7	218	1.61
p-dibromobenzene	87	218	1.57
o-toluic acid(邻甲基苯甲酸)	106	263	1.06
m-toluic acid	111	263	1.05
p-toluic acid	180	275	1.06
o-cresol(邻甲苯酚)	30	192	1.03
m-cresol	12	202	1.03
p-cresol	36	202	1.03

The relative boiling points of many benzene derivatives are related to their dipole moments. For example, the dichlorobenzenes have boiling points that follow their dipole moments. Symmetrical *p*-dichlorobenzene has zero dipole moment and the lowest boiling point. *m*-Dichlorobenzene has a small dipole moment and a slightly higher boiling point. *o*-Dichlorobenzene has the largest dipole moment and the highest boiling point. Even though

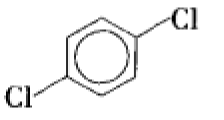
p-dichlorobenzene has the lowest boiling point, it packs best into a crystal, and it has the highest melting point of the dichlorobenzenes.



o-dichlorobenzene
bp 181 ℃
mp −17 ℃



m-dichlorobenzene
bp 173 ℃
mp −25 ℃



p-dichlorobenzene
bp 170 ℃
mp 54 ℃

Benzene and other aromatic hydrocarbons are slightly denser than the nonaromatic analogues, but they are still less dense than water. The halogenated benzenes are denser than water. Aromatic hydrocarbons and halogenated aromatics are generally insoluble in water, although some derivatives with strongly polar functional groups (phenol, benzoic acid, etc.) are moderately soluble in water.

17−13 Spectroscopy of Aromatic Compounds

Infrared Spectroscopy Aromatic compounds are readily identified by their infrared spectra because they show a characteristic C═C stretch around 1 600 cm^{-1}. This is a lower C═C stretching frequency than for isolated alkenes (1 640 to 1 680 cm^{-1}) or conjugated dienes (1 620 to 1 640 cm^{-1}) because the aromatic bond order is only about $1\frac{1}{2}$. The aromatic bond is therefore less stiff than a normal double bond, and it vibrates at a lower frequency.

Like alkenes, aromatic compounds show unsaturated ═C—H stretching just above 3 000 cm^{-1} (usually around 3 030 cm^{-1}). The combination of the aromatic C═C stretch around 1 600 cm^{-1} and the ═C—H stretch just above 3 000 cm^{-1} leaves little doubt of the presence of an aromatic ring.

NMR Spectroscopy Aromatic compounds give readily identifiable ^1H NMR signals around $\delta7$ to $\delta8$, strongly deshielded by the aromatic ring current. In benzene, the aromatic protons absorb around $\delta7.2$. The signals may be moved farther downfield by electron-withdrawing groups such as carbonyl, nitro, or cyano groups, or upfield by electron-donating groups such as hydroxyl, alkoxy, or amino groups.

Nonequivalent aromatic protons that are ortho or meta usually split each other. The spin-spin splitting constants are about 8 Hz for ortho protons and 2 Hz for meta protons.

Aromatic carbon atoms absorb around $\delta120$ to $\delta150$ in the ^{13}C NMR spectrum. Alkene carbon atoms can also absorb in this spectral region, but the combination of ^{13}C NMR with ^1H NMR or IR spectroscopy usually leaves no doubt about the presence of an aromatic ring.

Ultraviolet Spectroscopy The ultraviolet spectra of aromatic compounds are quite different from those of nonaromatic polyenes. For example, benzene has three absorptions in the ultraviolet region: an intense band at λ_{max} = 184 nm[κ = 68 000 L/(mol·cm)], a moderate band at λ_{max} = 204 nm [κ = 8 800 L/(mol·cm)], and a characteristic low-intensity band of multiple absorptions centered around 254 nm [κ = 200 to 300 L/(mol·cm)].

Summary in Chinese

本章概要

一、苯的结构

苯是具有高度不饱和的环状闭合共轭体系，苯分子中的六个碳原子和六个氢原子都在一个平面内，是

正六边形平面分子，每个碳原子均以 sp^2 杂化轨道与相邻碳原子的 sp^2 杂化轨道形成 C—C σ 键，与氢原子的 s 轨道形成 C—H σ 键，每个碳原子的未杂化的 p 轨道互相平行且垂直于 σ 键所在的平面，侧面互相交叠形成完全离域的大 π 键。苯的离域能为 150 kJ/mol，体现了苯的热力学稳定性。

二、苯及其衍生物的物理性质

芳香烃不溶于水，易溶于有机溶剂；沸点随相对分子质量升高而升高，在相对分子质量相同的同分异构体中，沸点与其分子的偶极矩有关，例如在邻、间、对二氯苯中，由于邻二氯苯的偶极矩较大，故其沸点较间、对异构体高；熔点除与相对分子质量有关外，还与分子结构的对称性有关，通常对位异构体由于分子对称，熔点较高。

三、芳香性

1. 芳香性化合物：含有共轭 π 键的环状结构；环上每个原子有未杂化的 p 轨道；未杂化的 p 轨道相互交叠形成环状共轭闭合体系，为了有效交叠，结构必须是平面或近似平面的；环上 π 电子的离域必须降低体系能量。

2. Hückel 规则：具有平面、环状共轭体系、π 电子数目为 $4N+2$（N 为自然数）的化合物是芳香性化合物；如果共轭体系的电子数为 $4N$，则该化合物是反芳香性化合物。一般情况下，当 $N \geqslant 7$ 时，Hückel 规则不适用；$N=2$ 的[10]轮烯，由于环上碳原子不能在同一平面，也无芳香性。

Hückel 规则可用于判断轮烯、杂环化合物、稠环、稠杂环、环状离子等是否有芳香性。

四、芳香杂环化合物

1. 呋喃、噻吩、吡咯是重要的五元杂环化合物，其杂原子为 sp^2 杂化，p 轨道上的一对电子与四个 sp^2 杂化的碳原子 p 轨道上的单电子组成了大 π 键（π_5^6），符合 Hückel 规则，具有芳香性，其化学性质与苯类似。

2. 吡啶是重要的六元杂环化合物，其氮原子为 sp^2 杂化，p 轨道上的单电子与环上其他五个 sp^2 杂化的碳原子 p 轨道上单电子组成了大 π 键（π_6^6），符合 Hückel 规则，具有芳香性。吡啶分子中氮原子的 sp^2 杂化轨道上有一对未成键电子，吡啶具有碱性，可以与质子（Lewis 酸）形成吡啶盐。而吡咯分子中氮原子上的孤对电子在 p 轨道上，参加了共轭大 π 键的形成，如果与质子结合，将破坏大 π 键，吡咯环失去芳香性，所以吡咯的碱性极弱。

Essential Problem-Solving Skills in Chapter 17

1. Be able to construct the molecular orbitals of a cyclic system of p orbitals similar to benzene and cyclobutadiene.
2. Use the polygon rule to draw the energy diagram for a cyclic system of p orbitals, and fill in the electrons to show whether a given compound or ion is aromatic or antiaromatic.
3. Use Hückel's rule to predict whether a given annulene, heterocycle, or ion will be aromatic, antiaromatic, or nonaromatic.
4. For heterocycles containing nitrogen atoms, determine whether the lone pairs are used in the aromatic system, and predict whether the nitrogen atom is strongly or weakly basic.
5. Recognize fused aromatic systems such as polynuclear aromatic hydrocarbons and fused heterocyclic compounds, and use the theory of aromatic compounds to explain their properties.
6. Name aromatic compounds, and draw their structures from the names.
7. Use IR, NMR, UV, and mass spectra to determine the structures of aromatic compounds. Given an aromatic compound, predict the important features of its spectra.

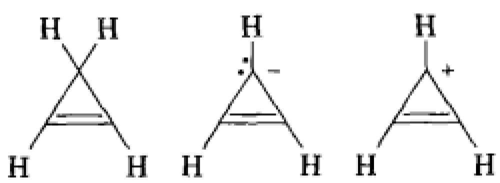
Study Problems

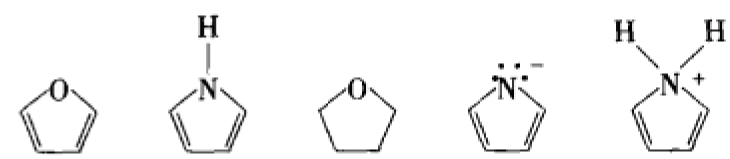
17-11 Define each term and give an example.

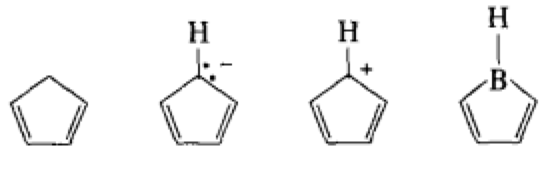
(**a**) a heterocyclic aromatic compound
(**b**) an antiaromatic compound
(**c**) a Kekulé structure
(**d**) an annulene
(**e**) degenerate orbitals
(**f**) the polygon rule
(**g**) a polynuclear aromatic heterocycle
(**h**) fused rings
(**i**) a polynuclear aromatic hydrocarbon
(**j**) a filled shell of MOs
(**k**) Hückel's rule
(**l**) resonance energy
(**m**) an aryl group

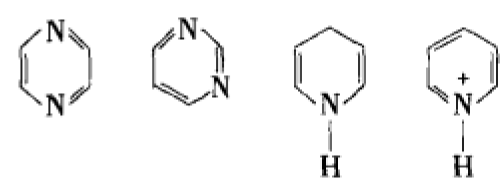
17−12 One of the following hydrocarbons is much more acidic than the others. Indicate which one, and explain why it is unusually acidic.

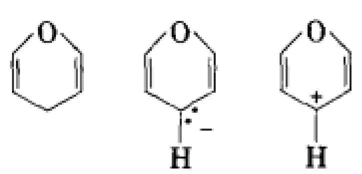
17−13 The following molecules and ions are grouped by similar structures. Classify each as aromatic, antiaromatic, or nonaromatic. For the aromatic and antiaromatic species, give the number of pi electrons in the ring.

(a) 

(b) 

(c) 

(d) 

(e) 

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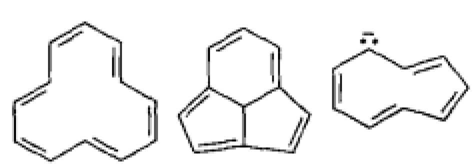
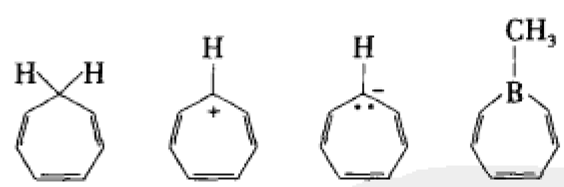
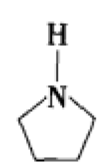
(g) 

(h) 

17−14 Each of the following heterocycles includes one or more nitrogen atoms. Classify each nitrogen atom as strongly basic or weakly basic, according to the availability of its lone pair of electrons.

(a)

(b) 

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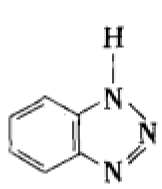
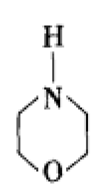
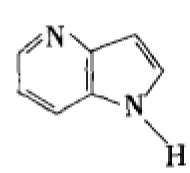
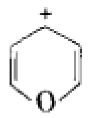
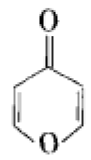
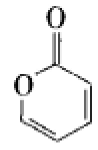
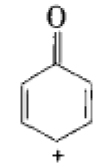
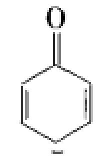
(d) 

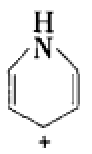
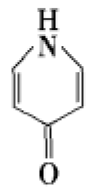
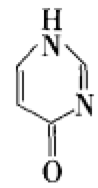
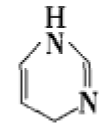
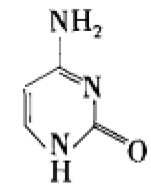
(e) 

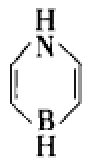
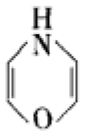
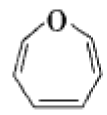
(f) 

***17−15** Some of the following compounds show aromatic properties, and others do not.

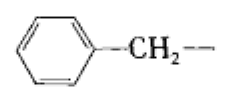
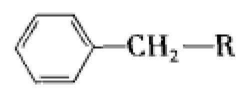
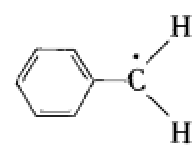
1. Predict which ones are likely to be aromatic, and explain why they are aromatic.
2. Predict which nitrogen atoms are more basic than water and which are less basic.

(a)  (b)  (c)  (d)  (e) 

(f)  (g)  (h)  (i)  (j) 

(k)  (l)  (m) 

*17-16 The benzene ring alters the reactivity of a neighboring group in the *benzylic position* much like a double bond alters the reactivity of groups in the allylic position.

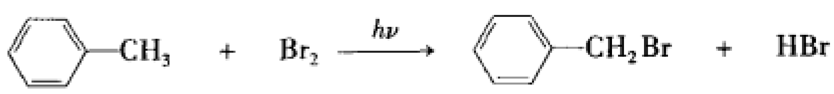
$H_2C{=}CH{-}CH_2{-}R$   

allylic position | benzyl group | benzylic position | benzyl radical

Benzylic cations, anions, and radicals are all more stable than simple alkyl intermediates.

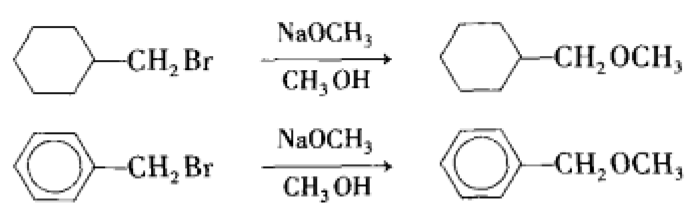
(a) Use resonance structures to show the delocalization (over four carbon atoms) of the positive charge, unpaired electron, and negative charge of the benzyl cation, radical, and anion.

(b) Toluene reacts with bromine in the presence of light to give benzyl bromide. Propose a mechanism for this reaction.

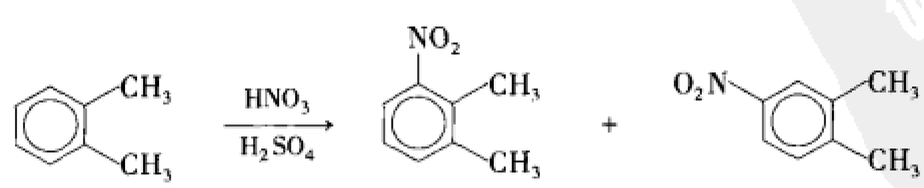


toluene | benzyl bromide

(c) Which of the following reactions will have the faster rate and give the better yield? Use a drawing of the transition state to explain your answer.



17-17 Before spectroscopy was invented, *Körner's absolute method* was used to determine whether a disubstituted benzene derivative was the ortho, meta, or para isomer. Körner's method involves adding a third group (often a nitro group) and determining how many isomers are formed. For example, when *o*-xylene is nitrated, two isomers are formed.

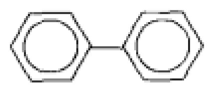


(a) How many isomers are formed by nitration of *m*-xylene?

(b) How many isomers are formed by nitration of *p*-xylene?

(c) A turn-of-the-century chemist isolated an aromatic compound of molecular formula $C_6H_4Br_2$. He carefully nitrated this compound and purified three isomers of formula $C_6H_3Br_2NO_2$. Propose structures for the original compound and the three nitrated derivatives.

17-18 Biphenyl has the following structure.



biphenyl(联苯)

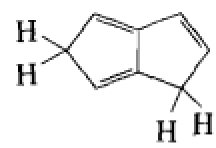
(a) Is biphenyl a (fused) polynuclear aromatic hydrocarbon?

(b) How many pi electrons are there in the two aromatic rings of biphenyl? How does this number compare with that for naphthalene?

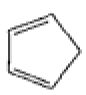
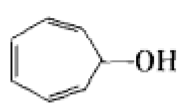
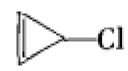
(c) The heat of hydrogenation for biphenyl is about 418 kJ/mol. Calculate the resonance energy of biphenyl.

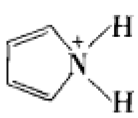
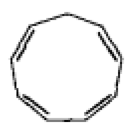
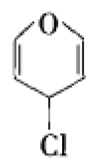
(d) Compare the resonance energy of biphenyl with that of naphthalene and with that of two benzene rings. Explain the difference in the resonance energies of naphthalene and biphenyl.

17−19 The following hydrocarbon reacts with two equivalents of butyllithium to form a dianion of formula $[C_8H_6]^{2-}$. Propose a structure for this dianion, and suggest why it forms so readily.

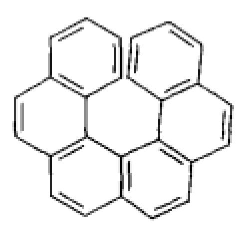
 $+ \ 2C_4H_9Li \longrightarrow [C_8H_6]^{2-}(Li^+)_2 \ + \ 2C_4H_{10}\uparrow$

17−20 How would you convert the following compounds to aromatic compounds?

(a)  **(b)**  **(c)** 

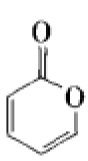
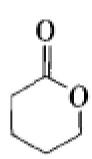
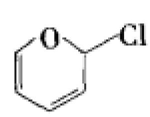
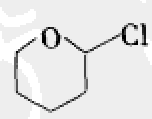
(d)  **(e)**  **(f)** 

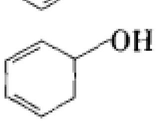
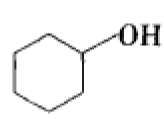
***17−21** Hexahelicene (adjacent) seems a poor candidate for optical activity because all its carbon atoms are sp^2 hybrids and presumably flat. Nevertheless, hexahelicene has been synthesized and separated into enantiomers. Its optical rotation is enormous: $[\alpha]_D = 3\,700°$. Explain why hexahelicene is optically active, and speculate as to why the rotation is so large.



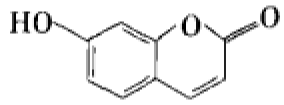
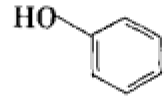
hexahelicene(六螺苯)

17−22 Four compounds are shown. These compounds react more quickly, or they react with more favorable equilibrium constants, than similar compounds with less conjugated systems. In each case, explain the enhanced reactivity.

(a)  is more basic than  **(b)**  ionizes more readily than 

(c)  dehydrates under much milder conditions than 

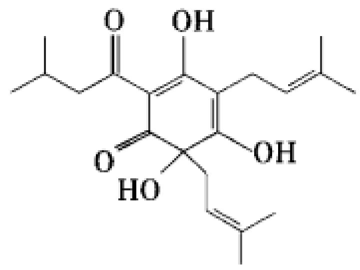
(d) Umbelliferone (7-hydroxycoumarin) is a common plant product that is used in sunscreen lotions.

 is more acidic than 

umbelliferone

(7-羟基香豆素)

17−23 Hops are added during the brewing of beer to provide bitter flavoring agents called the alpha-acids, or humulones. Humulon, one of the major humulones in hops, is used as a bacteriostatic agent that can survive autoclaving and retain its bacteriostatic effect. Is humulon aromatic?



humulon(葎草酮)

17−24 The proton NMR chemical shifts of the hydrogens in pyridine are shown. These are typical aromatic chemical shifts, except that the ortho protons (on the carbons bonded to nitrogen) are deshielded to δ8.60. A suitable oxidizing agent (such as a peroxyacid) can add an oxygen atom to pyridine to give pyridine *N*-oxide. The effect of this added oxygen atom is to shift the ortho protons *upfield* from δ8.60 to δ8.19. The meta protons are shifted *downfield* from δ7.25 to δ7.40. The para protons are shifted *upfield*, from δ7.64 to δ7.32. Explain this curious effect, shifting some protons upfield and others downfield.

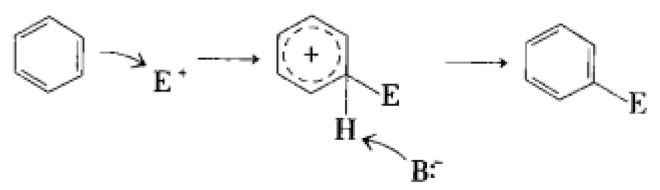
pyridine (吡啶) pyridine *N*-oxide (*N*−吡啶氧化物)

Chapter 18
Reactions of Aromatic Compounds

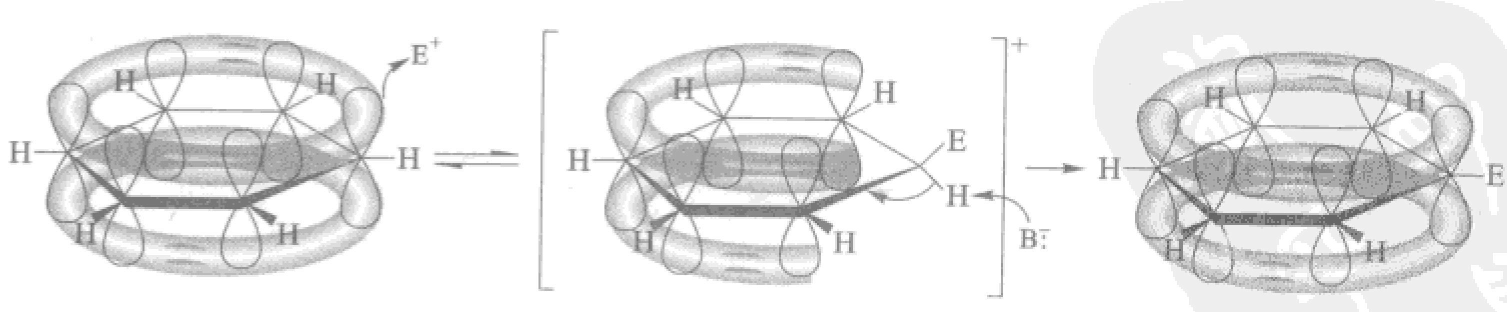
With an understanding of the properties that make a compound aromatic, we now consider the reactions of aromatic compounds. A large part of this chapter is devoted to *electrophilic aromatic substitution*, the most important mechanism involved in the reactions of aromatic compounds. Many reactions of benzene and its derivatives are explained by minor variations of electrophilic aromatic substitution. We will study several of these reactions and then consider how substituents on the ring influence its reactivity toward electrophilic aromatic substitution and the regiochemistry seen in the products. We will also study other reactions of aromatic compounds, including nucleophilic aromatic substitution, addition reactions, reactions of side chains, and special reactions of phenols.

18-1 Electrophilic Aromatic Substitution

Like an alkene, benzene has clouds of pi electrons above and below its sigma bond framework. Although benzene's pi electrons are in a stable aromatic system, they are available to attack a strong electrophile to give a carbocation. This resonance-stabilized carbocation is called a **sigma complex** because the electrophile is joined to the benzene ring by a new sigma bond.



sigma complex substituted



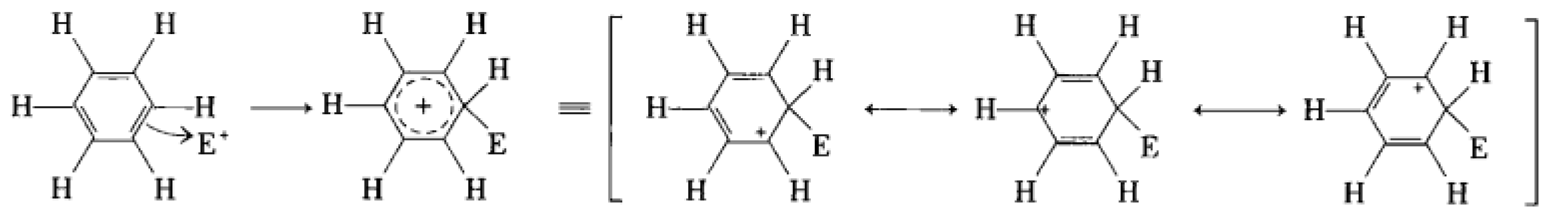
sigma complex substituted

The sigma complex (also called an *arenium ion*) is not aromatic because the sp^3-hybrid carbon atom interrupts the ring of p orbitals. This loss of aromaticity contributes to the highly endothermic nature of this first step. The sigma complex regains aromaticity either by a reversal of the first step (returning to the reactants) or by loss of the proton on the tetrahedral carbon atom, leading to the substitution product.

The overall reaction is the *substitution* of an electrophile (E^+) for a proton (H^+) on the aromatic ring: **electrophilic aromatic substitution.** This class of reactions includes substitutions by a wide variety of electrophilic reagents. Because it enables us to introduce functional groups directly onto the aromatic ring, electrophilic aromatic substitution is the most important method for synthesis of substituted aromatic compounds.

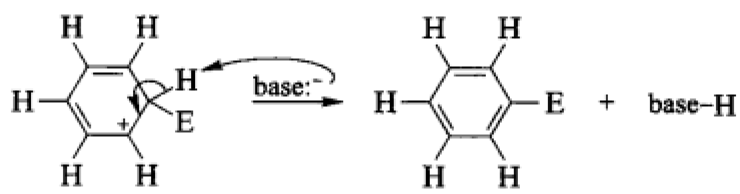
KEY MECHANISM 18－1 Electrophilic Aromatic Substitution

Step 1: Attack on the electrophile forms the sigma complex.



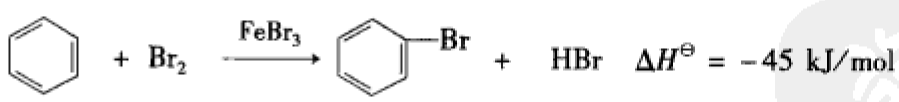
sigma complex (arenium ion)
(σ 络合物)

Step 2: Loss of a proton regains aromaticity and gives the substitution product.



18－2 Halogenation of Benzene

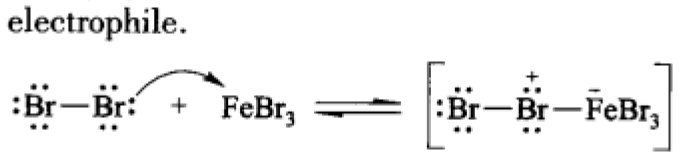
Bromination of Benzene Bromination follows the general mechanism for electrophilic aromatic substitution. Bromine itself is not sufficiently electrophilic to react with benzene, and the formation of Br^+ is difficult. A strong Lewis acid such as $FeBr_3$ catalyzes the reaction, however, by forming a complex with Br_2 that reacts much like Br^+. Bromine donates a pair of electrons to $FeBr_3$, forming a stronger electrophile with a weakened Br—Br bond and a partial positive charge on one of the bromine atoms. Attack by benzene forms the sigma complex. Bromide ion from $FeBr_4^-$ acts as a weak base to remove a proton from the sigma complex, giving the aromatic product and HBr, and regenerating the catalyst.



bromobenzene
(80%)

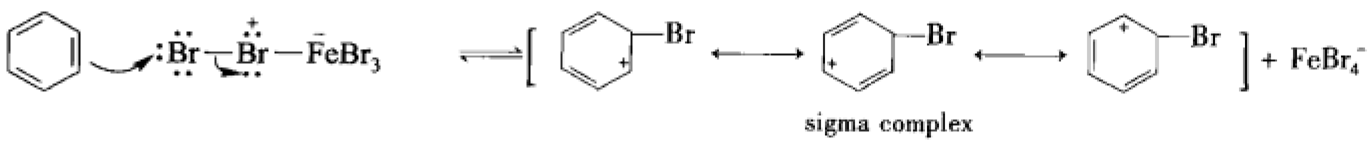
KEY MECHANISM 18－2 Bromination of Benzene

Step 1: Formation of a stronger electrophile.

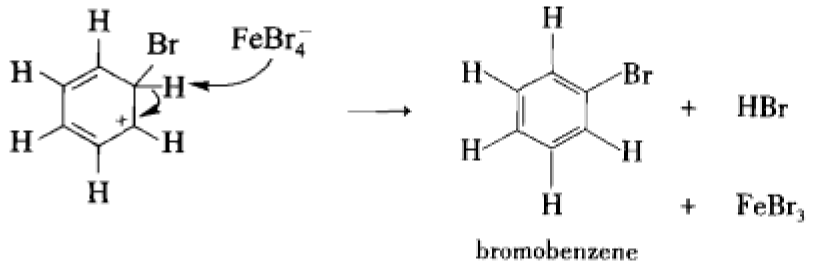


$Br_2 \cdot FeBr_3$ intermediate
(a stronger electrophile than Br_2)

Step 2: Electrophilic attack and formation of the sigma complex.



Step 3: Loss of a proton gives the products.



Formation of the sigma complex is rate-limiting, and the transition state leading to it occupies the highest-energy point on the energy diagram (Figure 18-1). This step is strongly endothermic because it forms a nonaromatic carbocation. The second step is exothermic because aromaticity is regained and a molecule of HBr is evolved. The overall reaction is exothermic by 45 kJ/mol.

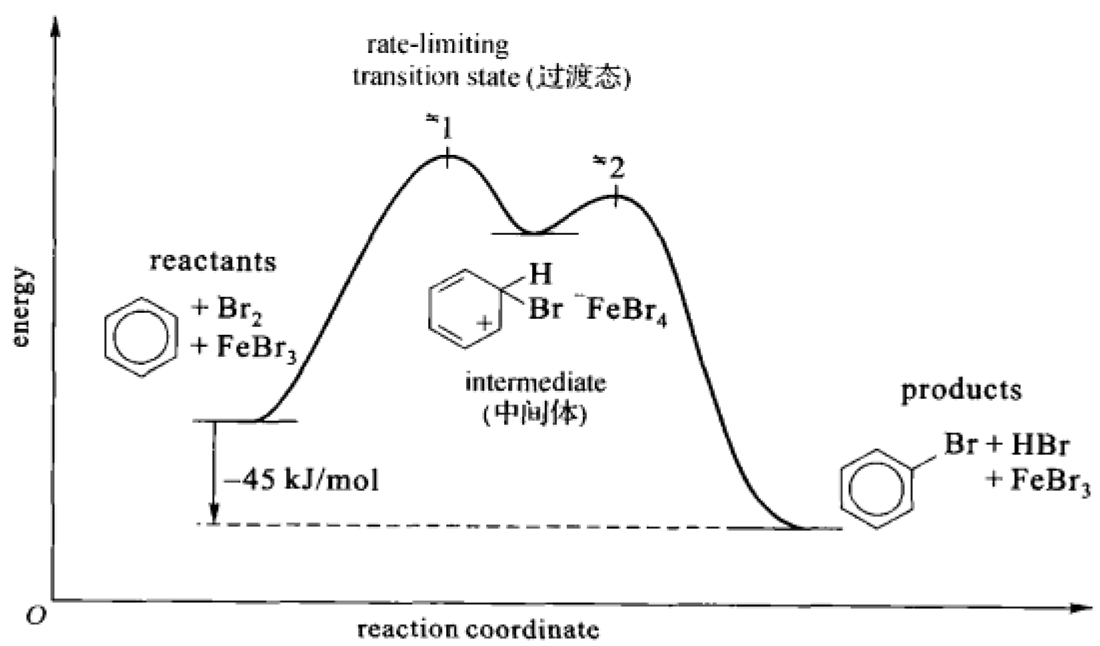


Figure 18−1 The energy diagram for the bromination of benzene.

Comparison with Alkenes Benzene is not as reactive as alkenes, which react rapidly with bromine at room temperature to give addition products. For example, cyclohexene reacts to give *trans*-1,2-dibromocyclohexane. This reaction is exothermic by about 121 kJ/mol.

The analogous addition of bromine to benzene is *endothermic* because it requires the loss of aromatic stability. The addition is not seen under normal circumstances. The *substitution* of bromine for a hydrogen atom gives an aromatic product. The substitution is exothermic, but it requires a Lewis acid catalyst to convert bromine to a stronger electrophile.

Chlorination of Benzene Chlorination of benzene works much like bromination, except that aluminum chloride ($AlCl_3$) is most often used as the Lewis acid catalyst.

benzene chlorobenzene (85%)

Iodination of Benzene Iodination of benzene requires an acidic oxidizing agent, such as nitric acid. Nitric acid is consumed in the reaction, so it is a reagent (an oxidant) rather than a catalyst.

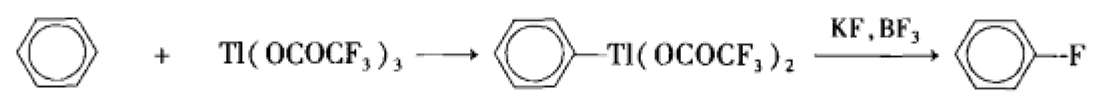
benzene iodobenzene (85%)

Iodination probably involves an electrophilic aromatic substitution with the iodine cation (I^+) acting as the electrophile. The iodine cation results from oxidation of iodine by nitric acid.

$$H^+ + HNO_3 + \frac{1}{2}I_2 \longrightarrow \underset{\text{iodine cation}}{I^+} + NO_2 + H_2O$$

PROBLEM 18−1

Controlled fluorination of benzene is difficult, but it can be accomplished by a two-step thallation procedure. Benzene reacts with thallium tris (trifluoroacetate), Tl $(OCOCF_3)_3$, to give an organothallium intermediate. Further reaction with potassium fluoride and boron trifluoride gives the aryl fluoride. Propose a mechanism for the first step, the thallation of benzene.



benzene thallium tris (trifluoroacetate) organothallium intermediate fluorobenzene

[*Hint*: The ionization of mercuric acetate gives the electrophile that oxymercurates an alkene; a similar ionization of thallium tris (trifluoroacetate) gives an electrophile that substitutes onto an aromatic ring.]

Thallation reactions are potentially useful, but organothallium compounds are highly toxic and easily absorbed through the skin.

18−3 Nitration of Benzene

Benzene reacts with hot, concentrated nitric acid to give nitrobenzene. This sluggish reaction is not convenient because a hot mixture of concentrated nitric acid with any oxidizable material might explode. A safer and more convenient procedure uses a mixture of nitric acid and sulfuric acid. Sulfuric acid is a catalyst, allowing nitration to take place more rapidly and at lower temperatures.

nitrobenzene (85%)
(硝基苯)

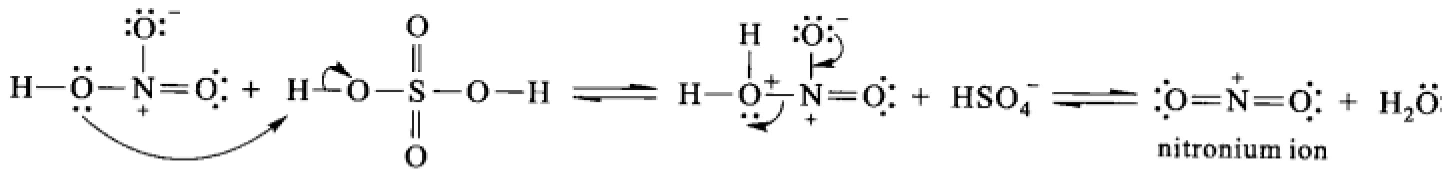
The mechanism is shown next. Sulfuric acid reacts with nitric acid to form the **nitronium ion** ($^+NO_2$), a powerful electrophile. The mechanism is similar to other sulfuric acid-catalyzed dehydrations. Sulfuric acid protonates

the hydroxyl group of nitric acid, allowing it to leave as water and form a nitronium ion. The nitronium ion reacts with benzene to form a sigma complex. Loss of a proton from the sigma complex gives nitrobenzene.

KEY MECHANISM 18-3 Nitration of Benzene

Preliminary steps: Formation of the nitronium ion, NO_2^+.

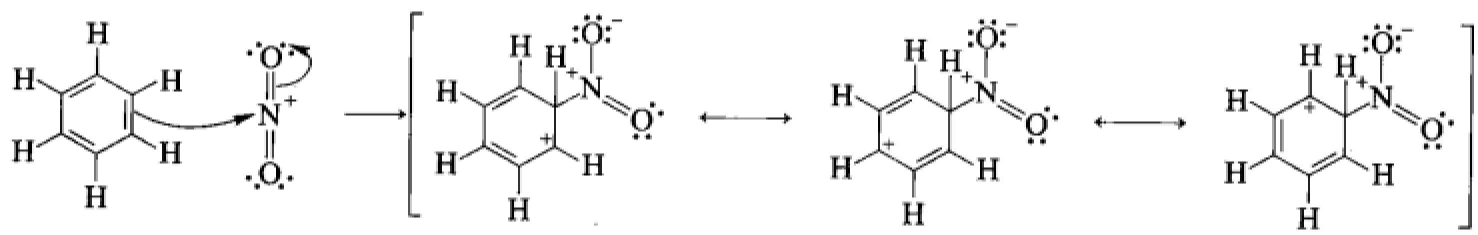
Nitric acid has a hydroxyl group that can protonate and leave as water, similar to the dehydration of an alcohol.



nitronium ion

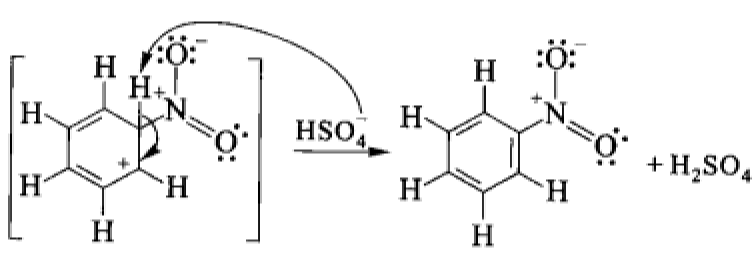
Electrophilic aromatic substitution by the nitronium ion gives nitrobenzene.

Step 1: Attack on the electrophile forms the sigma complex.



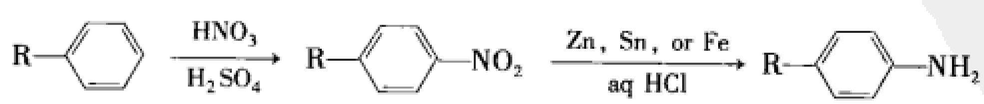
benzene   nitronium ion   sigma complex

Step 2: Loss of a proton gives nitrobenzene.



sigma complex (resonance-delocalized)   nitrobenzene

Aromatic nitro groups are easily reduced to amino ($—NH_2$) groups by treatment with an active metal such as tin, zinc, or iron in dilute acid. Nitration followed by reduction is often the best method for adding an amino group to an aromatic ring.

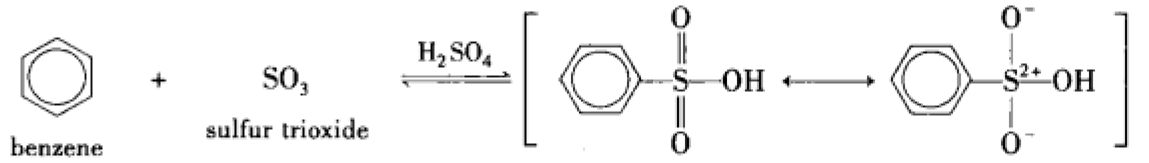


an alkylbenzene   a nitrated alkylbenzene   a substituted aniline

18-4 Sulfonation of Benzene

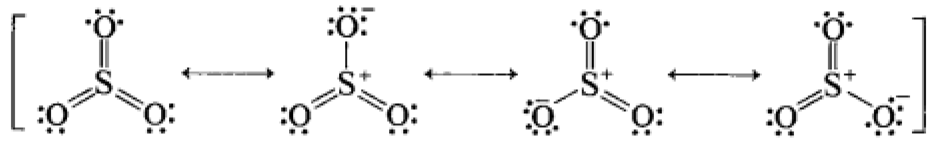
We have already used esters of *p*-toluenesulfonic acid as activated derivatives of alcohols with a good leaving group, the tosylate group. *p*-Toluenesulfonic acid is an example of an *arylsulfonic acid* (general formula Ar—

SO_3H), which are often used as strong acid catalysts that are soluble in nonpolar organic solvents. Arylsulfonic acids are easily synthesized by sulfonation of benzene derivatives, an electrophilic aromatic substitution using sulfur trioxide (SO_3) as the electrophile.



benzenesulfonic acid (95%)
(苯磺酸)

"Fuming sulfuric acid" is the common name for a solution of 7% SO_3 in H_2SO_4. Sulfur trioxide is the *anhydride* of sulfuric acid, meaning that the addition of water to SO_3 gives H_2SO_4. Although it is uncharged, sulfur trioxide is a strong electrophile, with three sulfonyl (S=O) bonds drawing electron density away from the sulfur atom. Benzene attacks sulfur trioxide, forming a sigma complex. Loss of a proton on the tetrahedral carbon and reprotonation on oxygen gives benzenesulfonic acid.

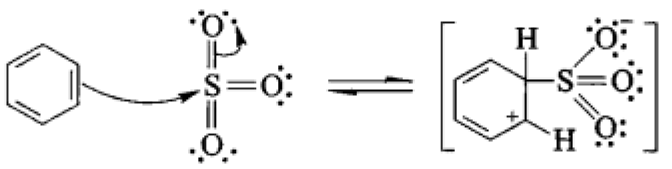


sulfur trioxide, a powerful electrophile

KEY MECHANISM 18-4 Sulfonation of Benzene

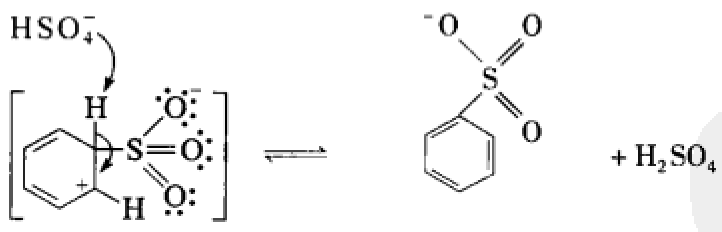
Sulfur trioxide is a powerful electrophile.

Step 1: Attack on the electrophile forms the sigma complex.



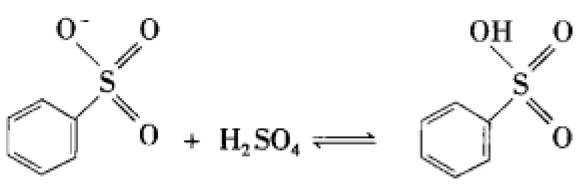
benzene sulfur trioxide sigma complex (resonance-delocalized)

Step 2: Loss of a proton regenerates an aromatic ring.



sigma complex benzenesulfonic acid

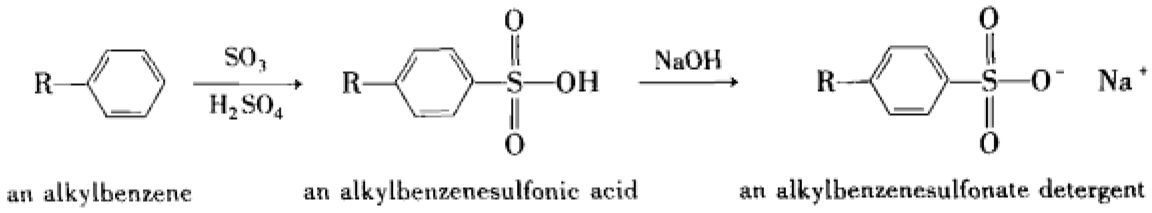
Step 3: The sulfonic acid group may become protonated in strong acid.



benzenesulfonic acid
(苯磺酸)

Sulfonation is economically important because alkylbenzene sulfonates are widely used as detergents. Sulfonation

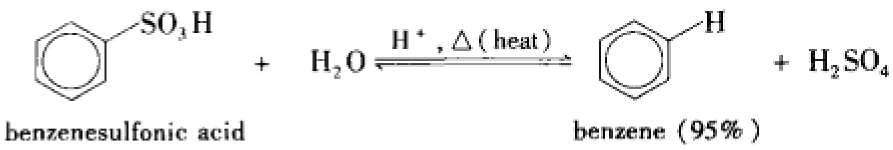
of an alkylbenzene (R = unbranched $C_{10}-C_{14}$) gives an alkylbenzenesulfonic acid, which is neutralized with base to give an alkylbenzene sulfonate detergent. Detergents are covered in more detail in Section 26-4.



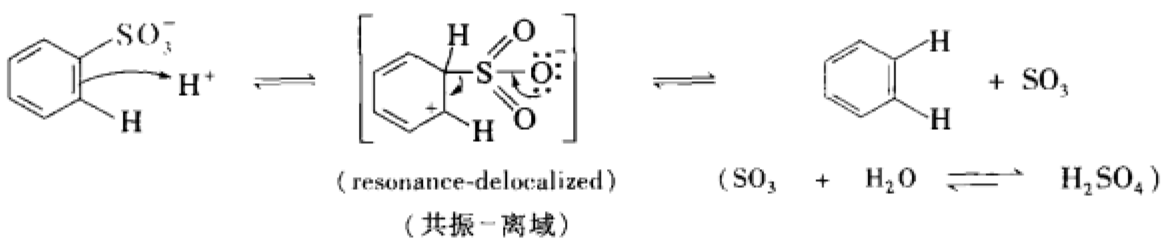
PROBLEM 18-2

Use resonance forms to show that the dipolar sigma complex shown in the sulfonation of benzene has its positive charge delocalized over three carbon atoms and its negative charge delocalized over three oxygen atoms.

Desulfonation Sulfonation is reversible, and a sulfonic acid group may be removed from an aromatic ring by heating in dilute sulfuric acid. In practice, steam is often used as a source of both water and heat for **desulfonation**.

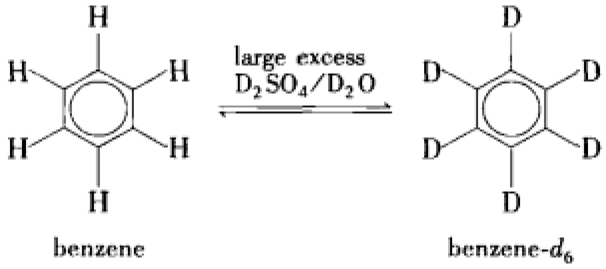


Desulfonation follows the same mechanistic path as sulfonation, except in the opposite order. A proton adds to a ring carbon to form a sigma complex, then loss of sulfur trioxide gives the unsubstituted aromatic ring.



Protonation of the Aromatic Ring; Hydrogen-Deuterium Exchange Desulfonation involves protonation of an aromatic ring to form a sigma complex. Similarly, if a proton attacks benzene, the sigma complex can lose either of the two protons at the tetrahedral carbon. We can prove that a reaction has occurred by using a deuterium ion (D^+) rather than a proton and by showing that the product contains a deuterium atom in place of hydrogen. This experiment is easily accomplished by adding SO_3 to some D_2O (heavy water) to generate D_2SO_4. Benzene reacts to give a deuterated product.

The reaction is reversible, but at equilibrium, the final products reflect the D/H ratio of the solution. A large excess of deuterium gives a product with all six of the benzene hydrogens replaced by deuterium. This reaction serves as a synthesis of benzene-d_6 (C_6D_6), a common NMR solvent.

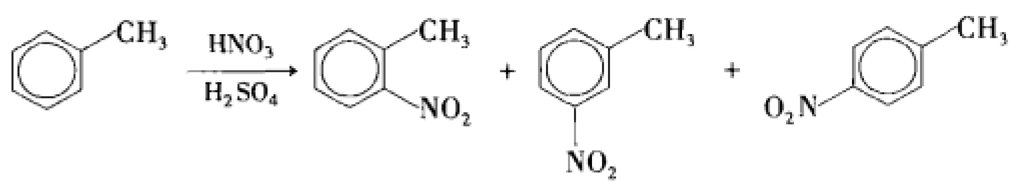


18−5 Nitration of Toluene: The Effect of Alkyl Substitution

Up to now, we have considered only benzene as the substrate for electrophilic aromatic substitution. To synthesize more complicated aromatic compounds, we need to consider the effects other substituents might have on further substitutions. For example, toluene (methylbenzene) reacts with a mixture of nitric and sulfuric acids much like benzene does, but with some interesting differences:

1. Toluene reacts about 25 times faster than benzene under the same conditions. We say that toluene is **activated** toward electrophilic aromatic substitution and that the methyl group is an **activating group**.

2. Nitration of toluene gives a mixture of products, primarily those resulting from substitution at the ortho and para positions. Because of this preference, we say that the methyl group of toluene is an **ortho, para-director.**



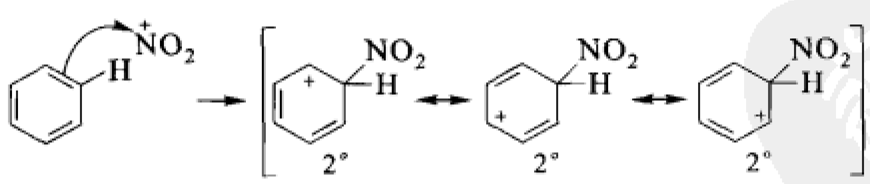
toluene | *o*-nitrotoluene (60%) | *m*-nitrotoluene (4%) | *p*-nitrotoluene (36%)

These product ratios show that the orientation of substitution is not random. If each C—H position were equally reactive, there would be equal amounts of ortho and meta substitution and half as much para substitution: 40% ortho, 40% meta, and 20% para. This is the statistical prediction based on the two ortho positions, two meta positions, and just one para position available for substitution.

The rate-limiting step (the highest-energy transition state) for electrophilic aromatic substitution is the first step, formation of the sigma complex. This step is where the electrophile bonds to the ring, determining the substitution pattern. We can explain both the enhanced reaction rate and the preference for ortho and para substitution by considering the structures of the intermediate sigma complexes. In this endothermic reaction, the structure of the transition state leading to the sigma complex resembles the product, the sigma complex. We are justified in using the stabilities of the sigma complexes to indicate the relative energies of the transition states leading to them.

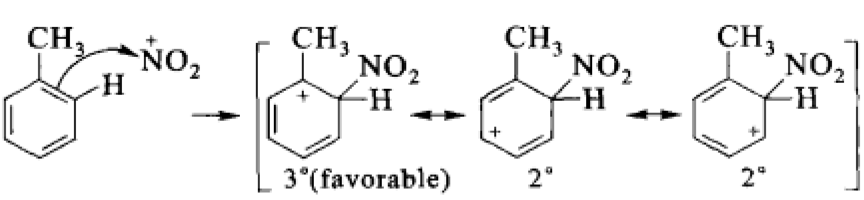
When benzene reacts with the nitronium ion, the resulting sigma complex has the positive charge distributed over three secondary (2°) carbon atoms.

Benzene

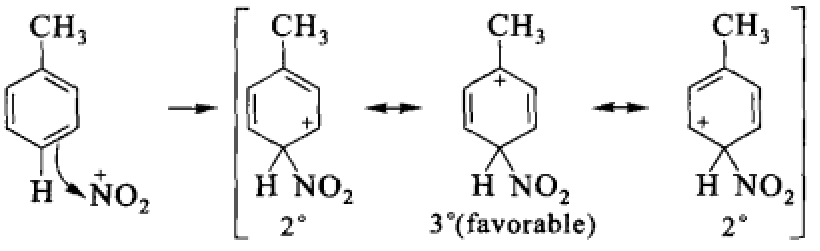


In ortho or para substitution of toluene, the positive charge is spread over two secondary carbons and one tertiary (3°) carbon (bearing the CH_3 group).

Ortho attack



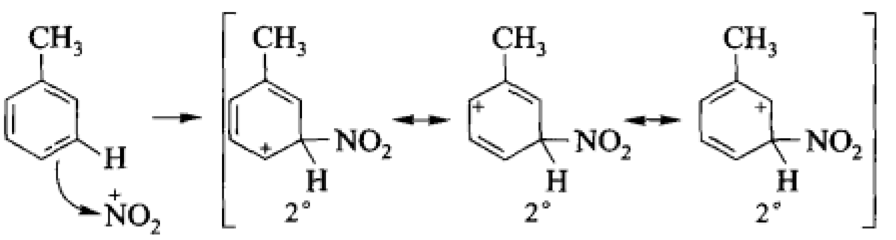
Para attack



Because the sigma complexes for ortho and para attack have resonance forms with tertiary carbocations, they are more stable than the sigma complex for nitration of benzene. Therefore, the ortho and para positions of toluene react faster than benzene.

The sigma complex for meta substitution has its positive charge spread over three 2°carbons; this intermediate is similar in energy to the intermediate for substitution of benzene. Therefore, meta substitution of toluene does not show the large rate enhancement seen with ortho and para substitution.

Meta attack



The methyl group in toluene is electron-donating; it stabilizes the intermediate sigma complex and the rate-limiting transition state leading to its formation. This stabilizing effect is large when it is situated ortho or para to the site of substitution and the positive charge is delocalized onto the tertiary carbon atom. When substitution occurs at the meta position, the positive charge is not delocalized onto the tertiary carbon, and the methyl group has a smaller effect on the stability of the sigma complex. Figure 18−2 compares the reaction-energy diagrams for nitration of benzene and toluene at the ortho, meta, and para positions.

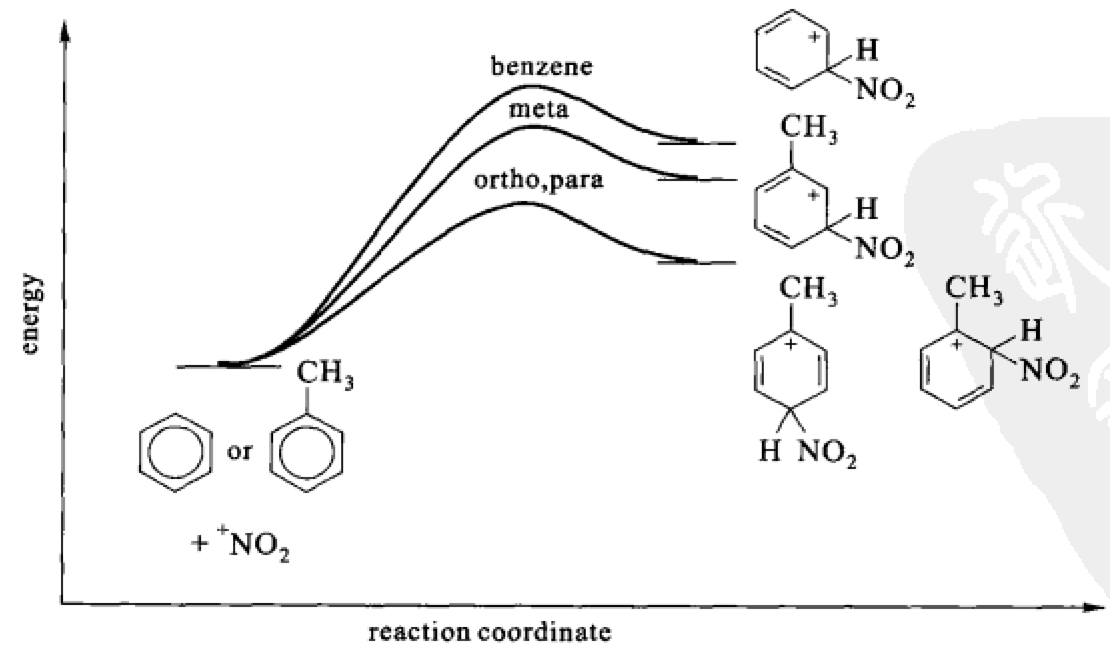


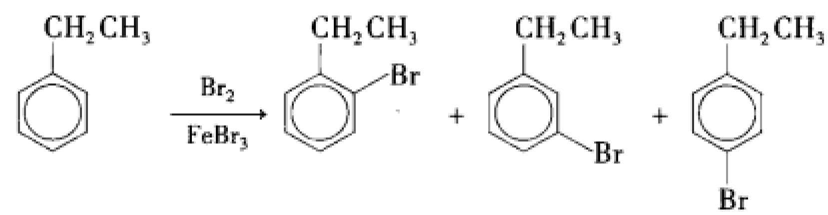
Figure 18−2 Energy profiles with an activating group.

18-6 Activating, Ortho, Para-Directing Substituents

18-6A Alkyl Groups

The results observed with toluene are general for any alkylbenzene undergoing electrophilic aromatic substitution. Substitution ortho or para to the alkyl group gives an intermediate (and a transition state) with the positive charge shared by the tertiary carbon atom. As a result, alkylbenzenes undergo electrophilic aromatic substitution faster than benzene, and the products are predominantly ortho-and para-substituted. An alkyl group is therefore an activating substituent, and it is **ortho, para-directing**. This effect is called **inductive stabilization** because the alkyl group donates electron density through the sigma bond joining it with the benzene ring.

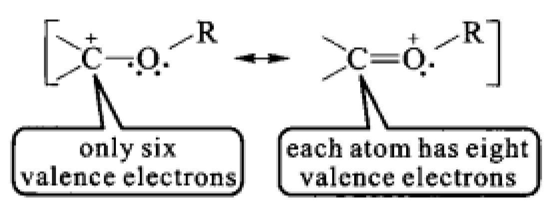
Shown next is the reaction of ethylbenzene with bromine, catalyzed by ferric bromide. As with toluene, the rates of formation of the ortho-and para-substituted isomers are greatly enhanced with respect to the meta isomer.



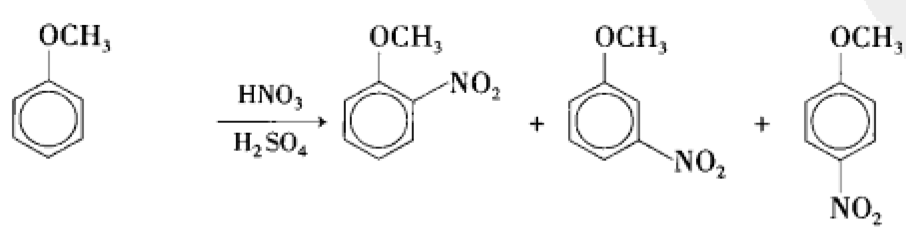
ethylbenzene — *o*-bromo (38%) — *m*-bromo (<1%) — *p*-bromo (62%)

18-6B Substituents with Nonbonding Electrons

Alkoxyl Groups Anisole (methoxybenzene) undergoes nitration about 10 000 times faster than benzene and about 400 times faster than toluene. This result seems curious because oxygen is a strongly electronegative group, yet it donates electron density to stabilize the transition state and the sigma complex. Recall that the nonbonding electrons of an oxygen atom adjacent to a carbocation stabilize the positive charge through resonance.



The second resonance form puts the positive charge on the electronegative oxygen atom, but it has more covalent bonds, and it provides each atom with an octet in its valence shell. This type of stabilization is called **resonance stabilization**, and the oxygen atom is called **resonance-donating** or **pi-donating** because it donates electron density through a pi bond in one of the resonance structures. Like alkyl groups, the methoxyl group of anisole preferentially activates the ortho and para positions.

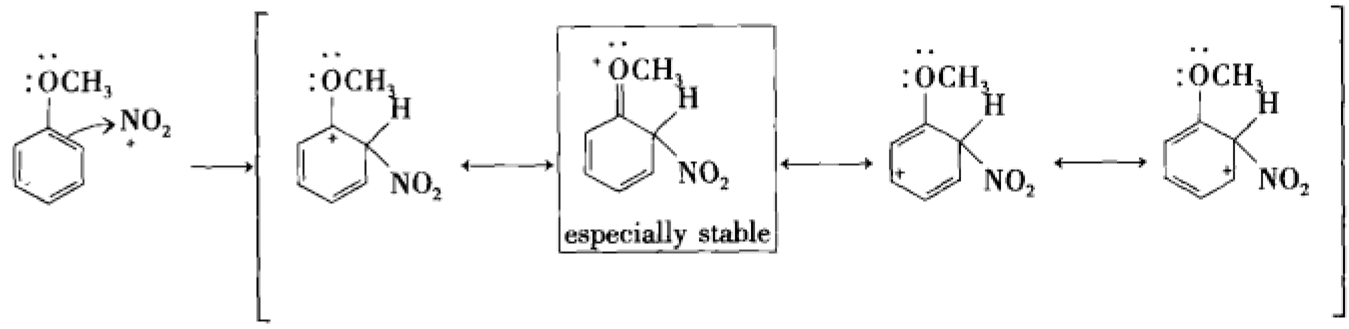


anisole (茴香醚,苯甲醚) — *o*-nitroanisole (31%) — *m*-nitroanisole (2%) — *p*-nitroanisole (67%)

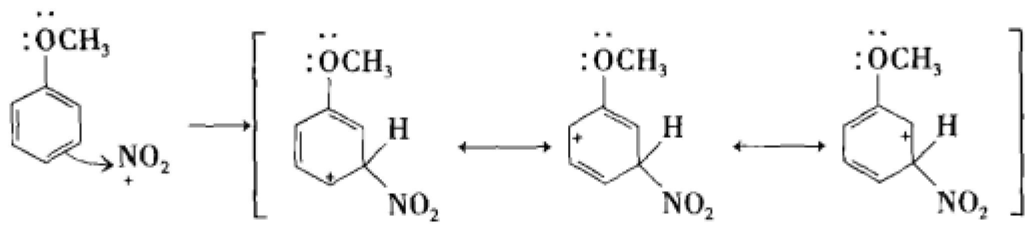
Resonance forms show that the methoxyl group effectively stabilizes the sigma complex if it is ortho or para to

the site of substitution, but not if it is meta. Resonance stabilization is provided by a pi bond between the —OCH_3 substituent and the ring.

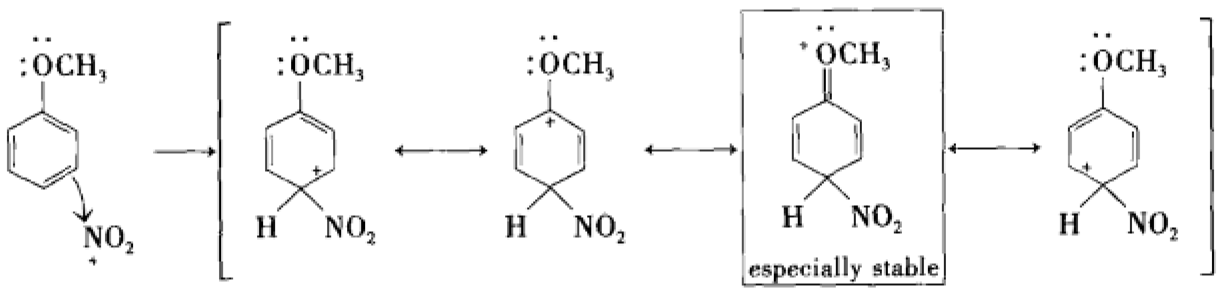
Ortho attack



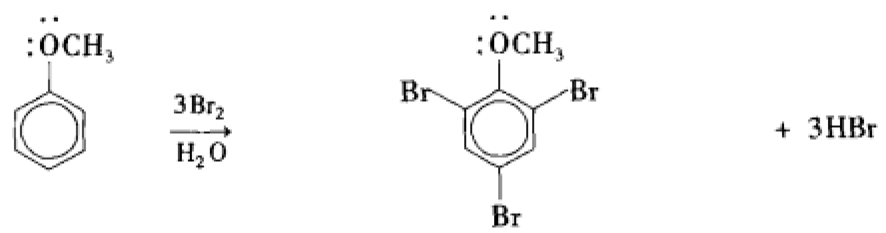
Meta attack



Para attack

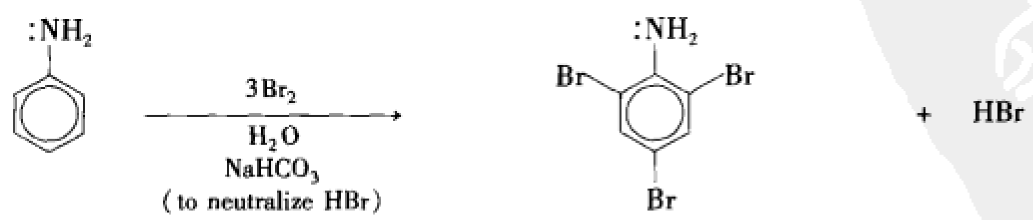


A methoxyl group is so strongly activating that anisole quickly brominates in water without a catalyst. In the presence of excess bromine, this reaction proceeds to the tribromide.



anisole（苯甲醚） 2,4,6-tribromoanisole（2,4,6−三溴苯甲醚）
（100%）

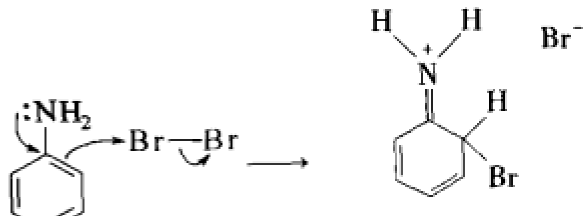
Amine Groups Like an alkoxyl group, a nitrogen atom with a nonbonding pair of electrons serves as a powerful activating group. For example, aniline undergoes a fast bromination (without a catalyst) in bromine water to give the tribromide. Sodium bicarbonate is added to neutralize the HBr formed and to prevent protonation of the basic amino (—NH_2) group.



aniline（苯胺） 2,4,6-tribromoaniline（2,4,6−三溴苯胺）
（100%）

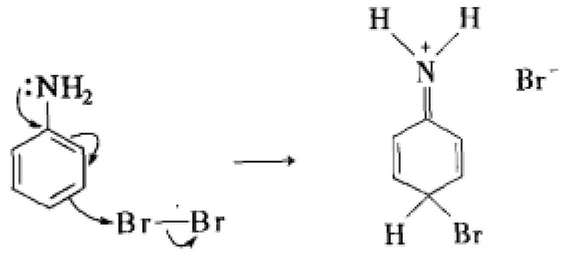
Nitrogen's nonbonding electrons provide resonance stabilization to the sigma complex if attack takes place ortho or para to the position of the nitrogen atom.

Ortho attack



(plus other resonance forms)

Para attack

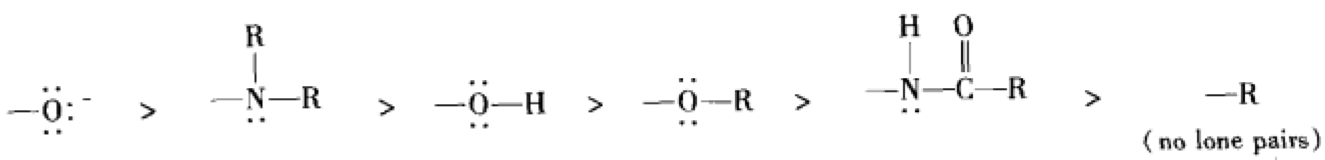


(plus other resonance forms)

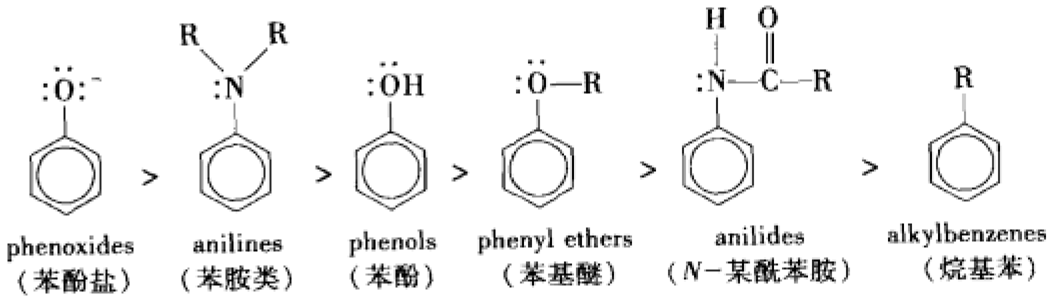
Thus, any substituent with a lone pair of electrons on the atom bonded to the ring can provide resonance stabilization to a sigma complex. Several examples are illustrated next in decreasing order of their activation of an aromatic ring. All these substituents are strongly activating, and they are all ortho, para-directing.

SUMMARY Activating, Ortho, Para-Directors

Groups

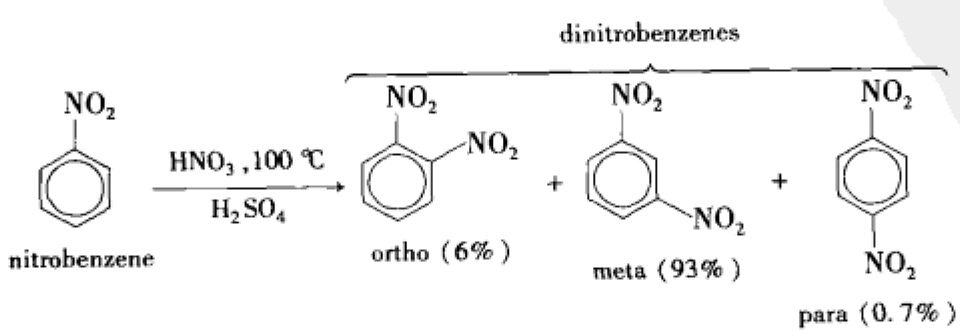


Compounds

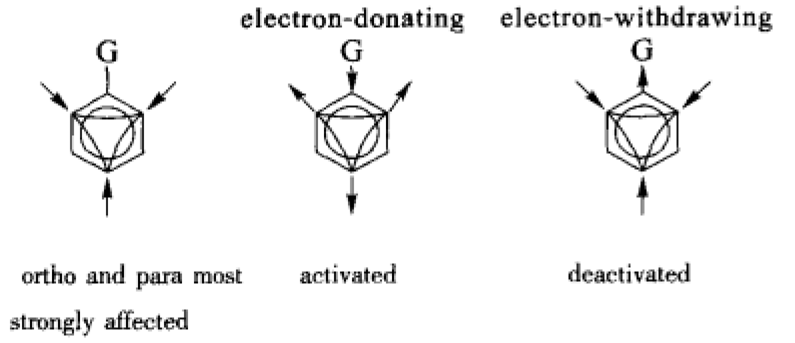


18-7 Deactivating, Meta-Directing Substituents

Nitrobenzene is about 100 000 times *less* reactive than benzene toward electrophilic aromatic substitution. For example, nitration of nitrobenzene requires concentrated nitric and sulfuric acids at temperatures above 100 ℃. Nitration proceeds slowly, giving the meta isomer as the major product.

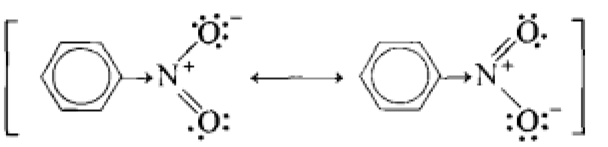


These results should not be surprising. We have already seen that a substituent on a benzene ring has its greatest effect on the carbon atoms ortho and para to the substituent. An electron-donating substituent activates primarily the ortho and para positions, and an electron-withdrawing substituent (such as a nitro group) deactivates primarily the ortho and para positions.



This selective deactivation leaves the meta positions the most reactive, and meta substitution is seen in the products. **Meta-directors**, often called **meta-allowing** substituents, deactivate the meta position less than the ortho and para positions, allowing meta substitution.

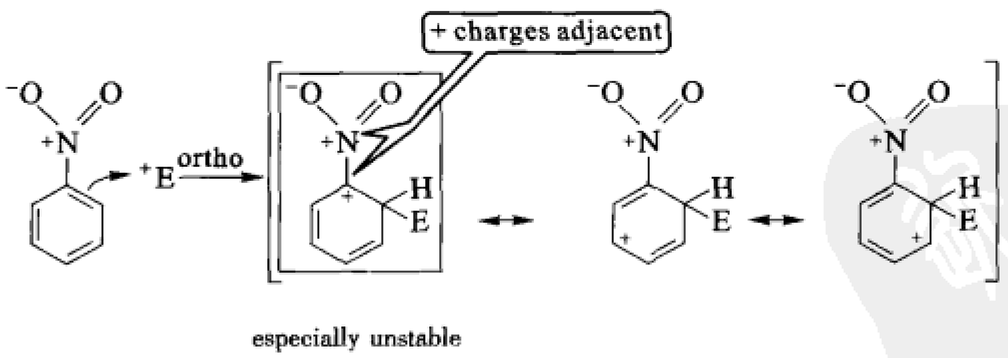
We can show why the nitro group is a strong **deactivating group** by considering its resonance forms. No matter how we position the electrons in a Lewis dot diagram, the nitrogen atom always has a formal positive charge.



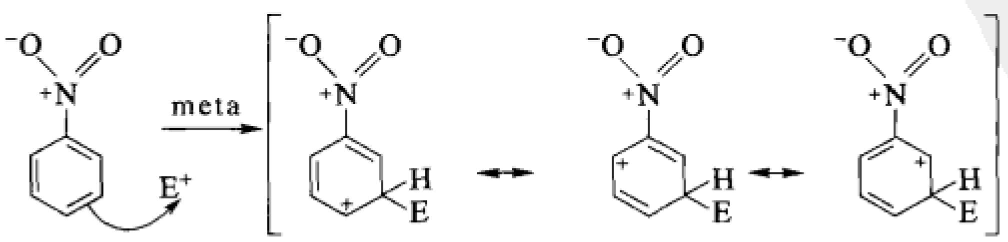
The positively charged nitrogen inductively withdraws electron density from the aromatic ring. This aromatic ring is less electron-rich than benzene, so it is deactivated toward reactions with electrophiles.

The following reactions show why this deactivating effect is strongest at the ortho and para positions. Each sigma complex has its positive charge spread over three carbon atoms. In ortho and para substitution, one of the carbon atoms bearing this positive charge is the carbon attached to the positively charged nitrogen atom of the nitro group. Since like charges repel, this close proximity of two positive charges is especially unstable.

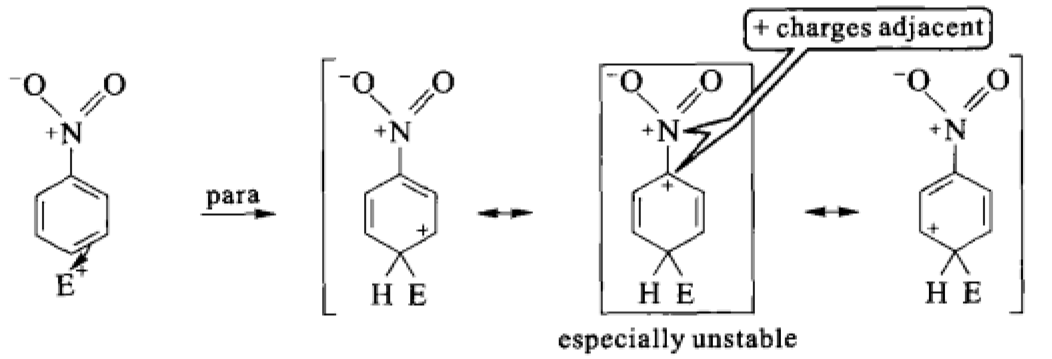
Ortho attack



Meta attack



Para attack



In the sigma complex for meta substitution, the carbon bonded to the nitro group does not share the positive charge of the ring. This is a more stable situation because the positive charges are farther apart. As a result, nitrobenzene reacts primarily at the meta position. We can summarize by saying that the nitro group is a deactivating group and that it is a meta-director (or meta-allower).

The energy diagram in Figure 18-3 compares the energies of the transition states and intermediates leading to ortho, meta, and para substitution of nitrobenzene with those for benzene. Notice that a higher activation energy is involved for substitution of nitrobenzene at any position, resulting in slower reaction rates than for benzene.

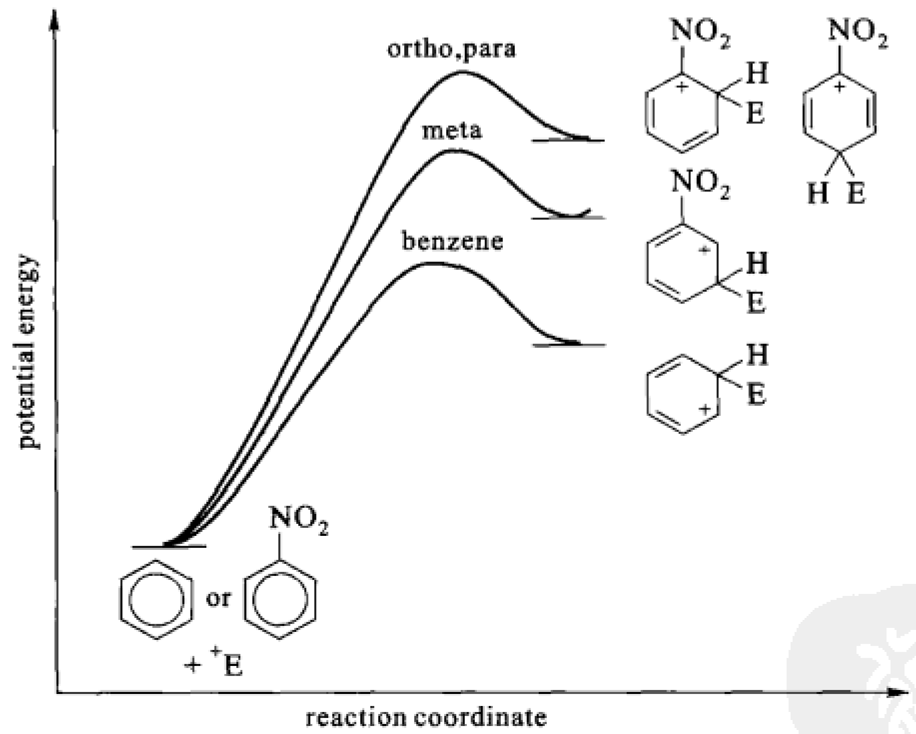
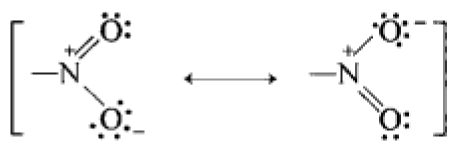
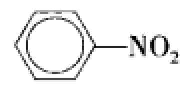
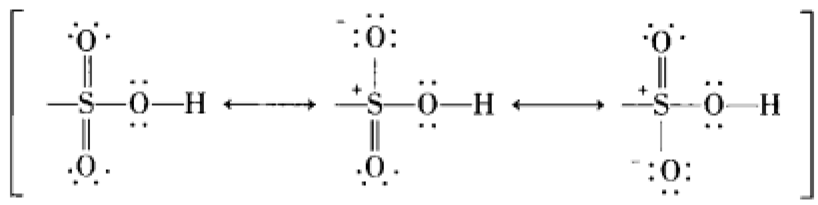
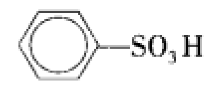
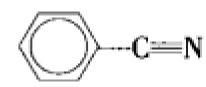
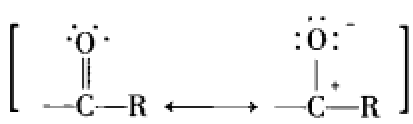
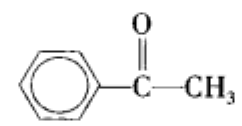
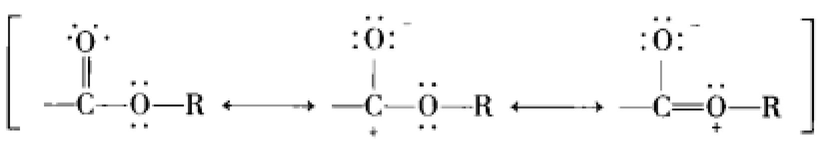
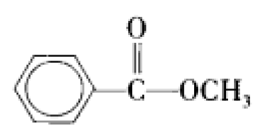
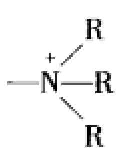
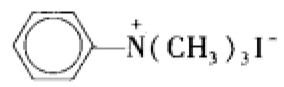


Figure 18-3 Energy profiles with a deactivating group.

Just as activating substituents are all ortho, para-directors, most deactivating substituents are meta-directors. In general, deactivating substituents are groups with a positive charge (or a partial positive charge) on the atom bonded to the aromatic ring. As we saw with the nitro group, this positively charged atom repels any positive charge on the adjacent carbon atom of the ring. Of the possible sigma complexes, only the one corresponding to meta substitution avoids putting a positive charge on this ring carbon.

The following summary table lists some common substituents that are deactivating and meta-directing. Resonance forms are also given to show how a positive charge arises on the atom bonded to the aromatic ring.

SUMMARY Deactivating, Meta-Directors

Group	*Resonance Forms*	*Example*
$—NO_2$ nitro		 nitrobenzene（硝基苯）
$—SO_3H$ sulfonic acid		 benzenesulfonic acid（苯磺酸）
—C≡N: cyano	[—C≡N: ⟷ $—\overset{+}{C}=\overset{-}{N}$:]	 benzonitrile（苄腈，苯基氰）
—C(=O)—R ketone or aldehyde		 acetophenone（乙酰苯，苯乙酮）
—C(=O)—O—R ester		 methyl benzoate（苯甲酸甲酯）
$—\overset{+}{N}R_3$ quaternary ammonium		 trimethylanilinium iodide（碘化三甲基苯铵）

PROBLEM 18−3

In an aqueous solution containing sodium bicarbonate, aniline reacts quickly with bromine to give 2,4,6-tribromoaniline. Nitration of aniline requires very strong conditions, however, and the yields (mostly *m*-nitroaniline) are poor.

(a) What conditions are used for nitration, and what form of aniline is present under these conditions?

(b) Explain why nitration of aniline is so sluggish and why it gives mostly meta substitution.

***(c)** Although nitration of aniline is slow and gives mostly meta substitution, nitration of acetanilide ($PhNHCOCH_3$) goes quickly and gives mostlsy para substitution. Use resonance forms to explain this difference in reactivity.

18−8 Halogen Substituents: Deactivating, but Ortho, Para-Directing

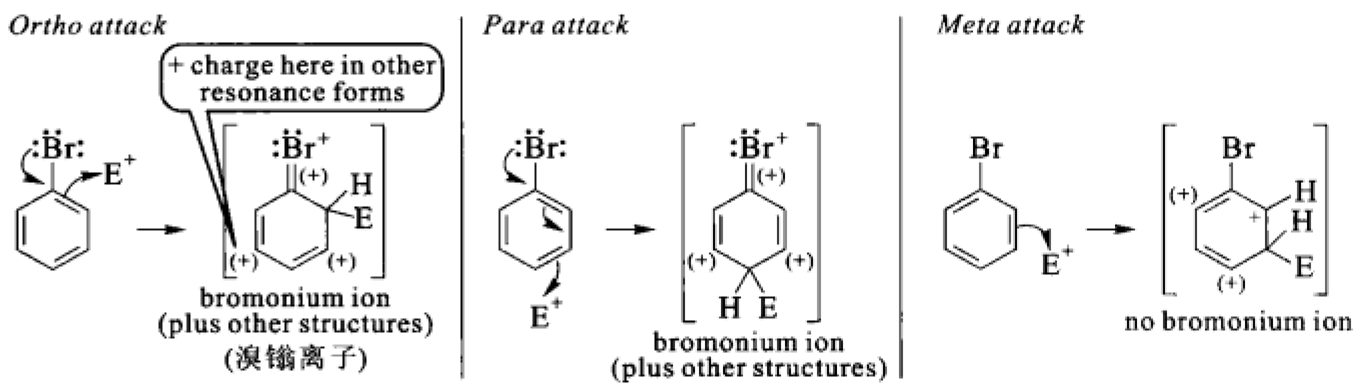
The halobenzenes are exceptions to the general rules. Halogens are deactivating groups, yet they are ortho, para-directors. We can explain this unusual combination of properties by considering that

1. the halogens are strongly electronegative, withdrawing electron density from a carbon atom through the sigma bond (inductive withdrawal), and

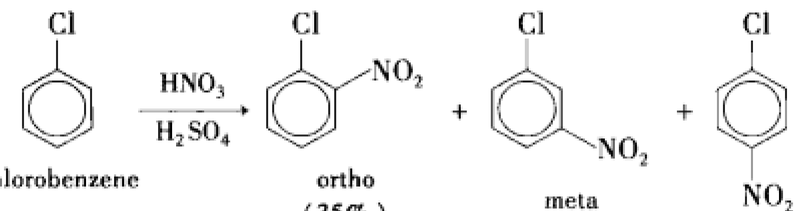
2. the halogens have nonbonding electrons that can donate electron density through pi bonding (resonance donation).

These inductive and resonance effects oppose each other. The carbon-halogen bond is strongly polarized, with the carbon atom at the positive end of the dipole. This polarization draws electron density away from the benzene ring, making it less reactive toward electrophilic substitution.

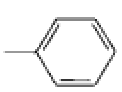
If an electrophile reacts at the ortho or para position, however, the positive charge of the sigma complex is shared by the carbon atom bearing the halogen. The nonbonding electrons of the halogen can further delocalize the charge onto the halogen, giving a **halonium ion** structure. This resonance stabilization allows a halogen to be pi-donating, even though it is sigma-withdrawing.



Reaction at the meta position gives a sigma complex whose positive charge is not delocalized onto the halogen-bearing carbon atom. Therefore, the meta intermediate is not stabilized by the halonium ion structure. The following reaction illustrates the preference for ortho and para substitution in the nitration of chlorobenzene.

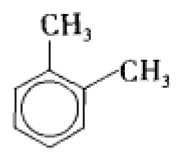


SUMMARY Directing Effects of Substituents

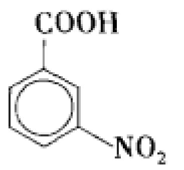
π Donors	*σ Donors*	*Halogens*	*Carbonyls*	*Other*
$-\ddot{N}H_2$	—R alkyl	—F	—C(=O)—R	$-SO_3H$
$-\ddot{O}H$	 aryl (weak pi donor)	—Cl	—C(=O)—OH	—C≡N
$-\ddot{O}R$		—Br	—C(=O)—OR	$-NO_2$
$-\ddot{N}HCOCH_3$		—I		$-\overset{+}{N}R_3$
ortho, para-directing			meta-directing	
ACTIVATING			DEACTIVATING	

18–9 Effects of Multiple Substituents on Electrophilic Aromatic Substitution

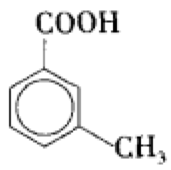
Two or more substituents exert a combined effect on the reactivity of an aromatic ring. If the groups reinforce each other, the result is easy to predict. For example, we can predict that all the xylenes (dimethylbenzenes) are activated toward electrophilic substitution because the two methyl groups are both activating. In the case of a nitrobenzoic acid, both substituents are deactivating, so we predict that a nitrobenzoic acid is deactivated toward attack by an electrophile.



o-xylene activated

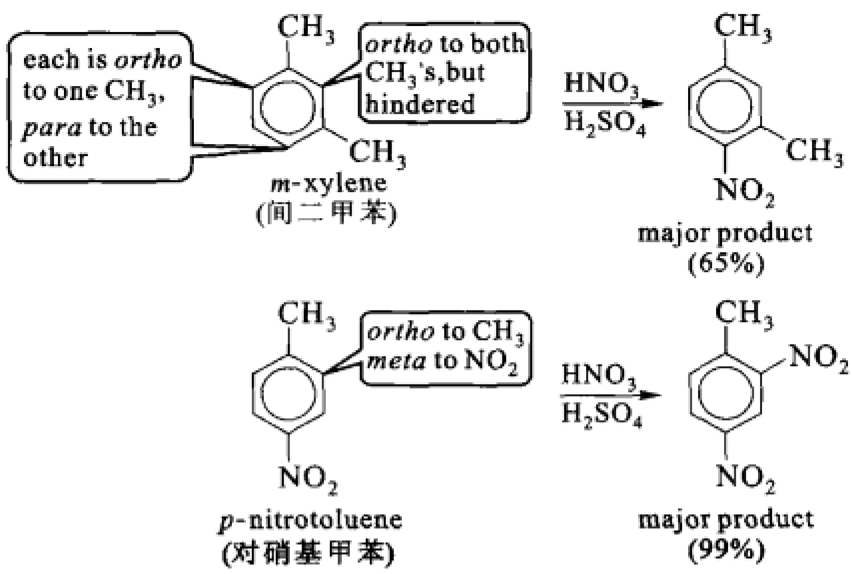


m-nitrobenzoic acid deactivated

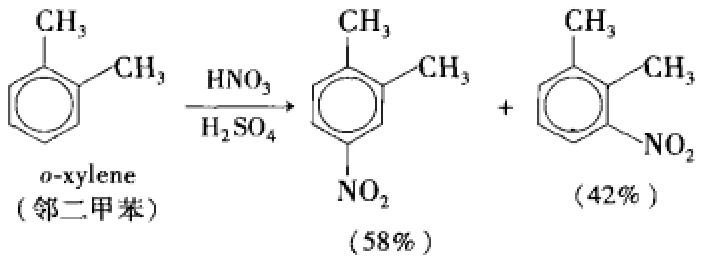


m-toluic acid not obvious

The orientation of addition is easily predicted in many cases. For example, in *m*-xylene there are two positions ortho to one of the methyl groups and para to the other. Electrophilic substitution occurs primarily at these two equivalent positions. There may be some substitution at the position between the two methyl groups (ortho to both), but this position is sterically hindered, and it is less reactive than the other two activated positions. In *p*-nitrotoluene, the methyl group directs an electrophile toward its ortho positions. The nitro group directs toward the same locations because they are its meta positions.



When the directing effects of two or more substituents conflict, it is more difficult to predict where an electrophile will react. In many cases, mixtures result. For example, *o*-xylene is activated at all the positions, so it gives mixtures of substitution products.



When there is a conflict between an activating group and a deactivating group, the activating group usually directs the substitution. We can make an important generalization:

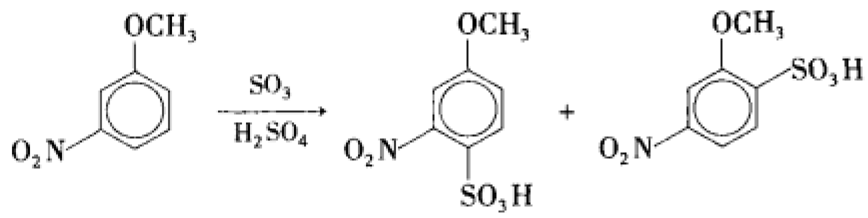
Activating groups are usually stronger directors than deactivating groups.

In fact, it is helpful to separate substituents into three classes, from strongest to weakest.

1. Powerful ortho, para-directors that stabilize the sigma complexes through resonance. Examples are —OH, —OR, and —NR_2 groups.
2. Moderate ortho, para-directors, such as alkyl groups and halogens.
3. All meta-directors.

$$—OH, —OR, —NR_2 > —R, —X > —\overset{O}{\overset{\|}{C}}—R, —SO_3H, —NO_2$$

If two substituents direct an incoming electrophile toward different reaction sites, the substituent in the stronger class predominates. If both are in the same class, mixtures are likely. In the following reaction, the stronger group predominates and directs the incoming substituent. The methoxyl group is a stronger director than the nitro group, and substitution occurs ortho and para to the methoxyl group. Steric effects prevent much substitution at the crowded position ortho to both the methoxyl group and the nitro group.

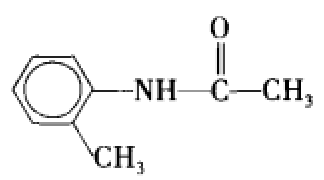


m-nitroanisole(间硝基苯甲醚) major products

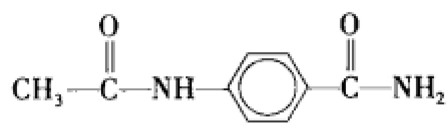
PROBLEM 18-4

Predict the mononitration products of the following aromatic compounds.

(a) *p*-methylanisole (b) *m*-nitrochlorobenzene
(c) *p*-chlorophenol (d) *m*-nitroanisole

(e) 

o-methylacetanilide

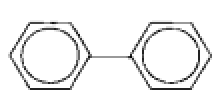
(f) 

(Consider the structures of these groups. One is activating, and the other is deactivating.)

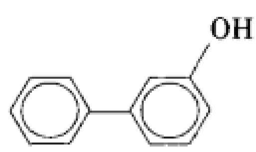
PROBLEM 18-5

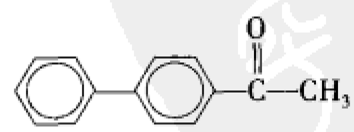
Biphenyl is two benzene rings joined by a single bond. The site of substitution for a biphenyl is determined by (1) which phenyl ring is more activated (or less deactivated), and (2) which position on that ring is most reactive, using the fact that a phenyl substituent is ortho, para-directing.

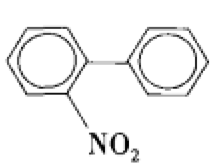
(a) Use resonance forms of a sigma complex to show why a phenyl substituent should be ortho, para-directing.
(b) Predict the mononitration products of the following compounds.

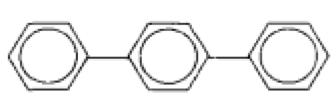
(i) 

biphenyl

(ii) 

(iii) 

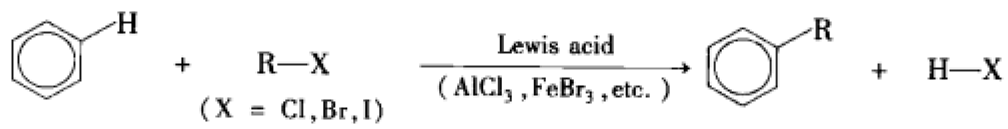
(iv) 

(v) 

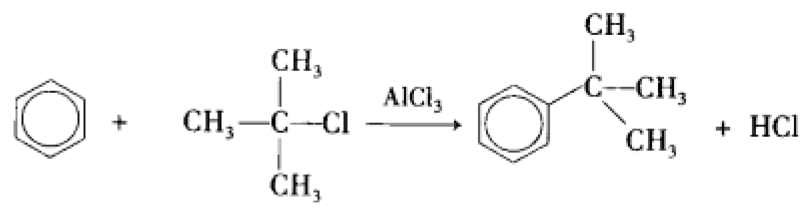
18−10 The Friedel-Crafts Alkylation

Carbocations are perhaps the most important electrophiles capable of substituting onto aromatic rings, because this substitution forms a new carbon-carbon bond. Reactions of carbocations with aromatic compounds were first studied in 1877 by the French alkaloid chemist Charles Friedel and his American partner, James Crafts. In the presence of Lewis acid catalysts such as aluminum chloride ($AlCl_3$) or ferric chloride ($FeCl_3$), alkyl halides were found to alkylate benzene to give alkylbenzenes. This useful reaction is called the **Friedel-Crafts alkylation.**

Friedel-Crafts alkylation



For example, aluminum chloride catalyzes the alkylation of benzene by *t*-butyl chloride. HCl gas is evolved.



benzene *t*-butyl chloride *t*-butylbenzene (90%)

This alkylation is a typical electrophilic aromatic substitution, with the *t*-butyl cation acting as the electrophile. The *t*-butyl cation is formed by reaction of *t*-butyl chloride with the catalyst, aluminum chloride. The *t*-butyl cation reacts with benzene to form a sigma complex. Loss of a proton gives the product, *t*-butylbenzene. The aluminum chloride catalyst is regenerated in the final step.

Friedel-Crafts alkylations are used with a wide variety of primary, secondary, and tertiary alkyl halides. With secondary and tertiary halides, the reacting electrophile is probably the carbocation.

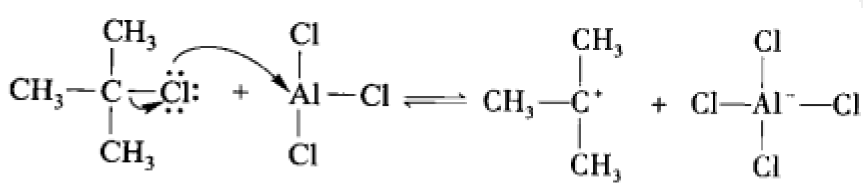
$$\underset{\text{(R is secondary or tertiary)}}{R{-}X} + AlCl_3 \rightleftharpoons \underset{\text{reacting electrophile}}{R^+} + X{-}^{-}AlCl_3$$

KEY MECHANISM 18−5 Friedel-Crafts Alkylation

Friedel-Crafts alkylation is an electrophilic aromatic substitution in which an alkyl cation acts as the electrophile.

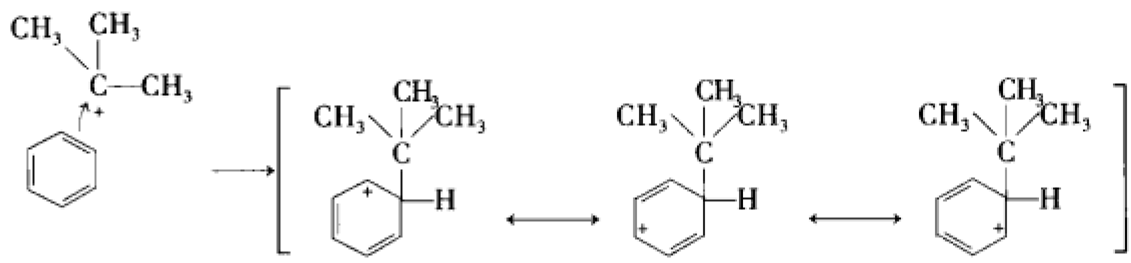
EXAMPLE: Alkylation of benzene by the *t*-butyl cation.

***Step 1*:** Formation of a carbocation.



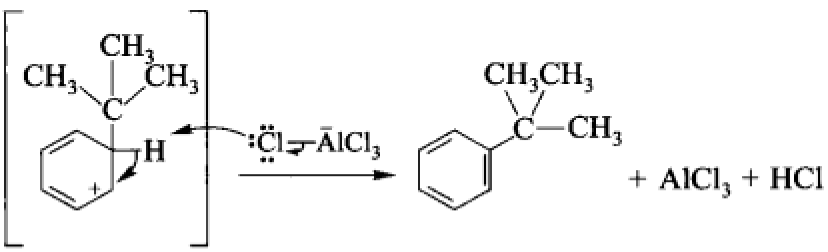
t-butyl chloride *t*-butyl cation

***Step 2*:** Electrophilic attack forms a sigma complex.



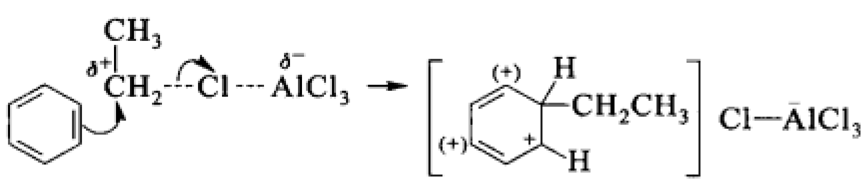
sigma complex

***Step 3*:** Loss of a proton regenerates the aromatic ring and gives the alkylated product.

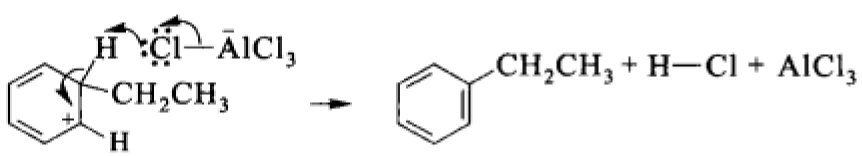


With primary alkyl halides, the free primary carbocation is too unstable. The actual electrophile is a complex of aluminum chloride with the alkyl halide. In this complex, the carbon-halogen bond is weakened (as indicated by dashed lines) and there is considerable positive charge on the carbon atom. The mechanism for the aluminum chloride-catalyzed reaction of ethyl chloride with benzene is as follows:

$$CH_3-CH_2-Cl + AlCl_3 \rightleftharpoons CH_3-\overset{\delta^+}{C}H_2\cdots Cl\cdots \overset{\delta^-}{A}lCl_3$$

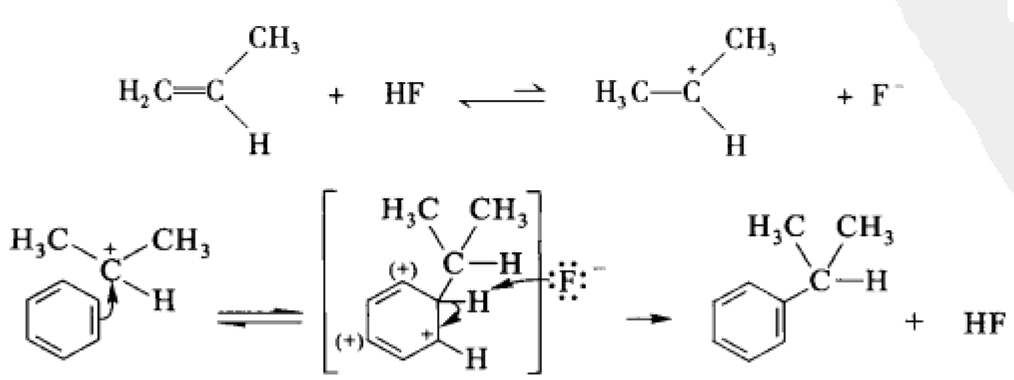


sigma complex



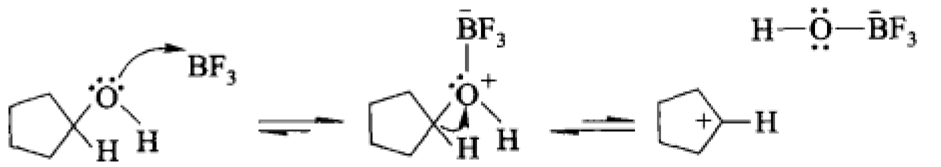
Friedel-Crafts Alkylation Using Other Carbocation Sources We have seen several ways of generating carbocations, and most of these can be used for Friedel-Crafts alkylations. Two common methods are protonation of alkenes and treatment of alcohols with BF_3.

Alkenes are protonated by HF to give carbocations. Fluoride ion is a weak nucleophile and does not immediately attack the carbocation. If benzene (or an activated benzene derivative) is present, electrophilic substitution occurs. The protonation step follows Markovnikov's rule, forming the more stable carbocation, which alkylates the aromatic ring.

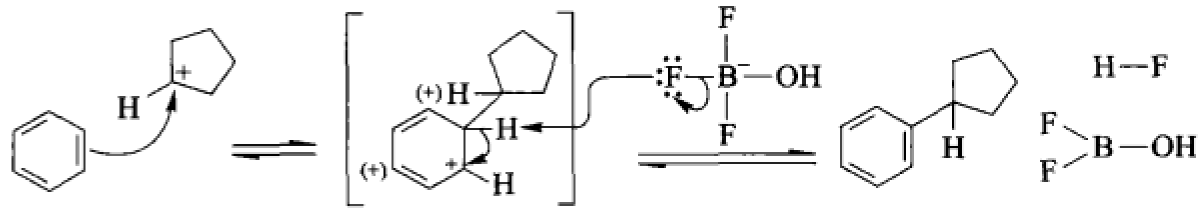


Alcohols are another source of carbocations for Friedel-Crafts alkylations. Alcohols commonly form carbocations when treated with Lewis acids such as boron trifluoride (BF_3). If benzene (or an activated benzene derivative) is present, substitution may occur.

Formation of the cation



Electrophilic substitution on benzene



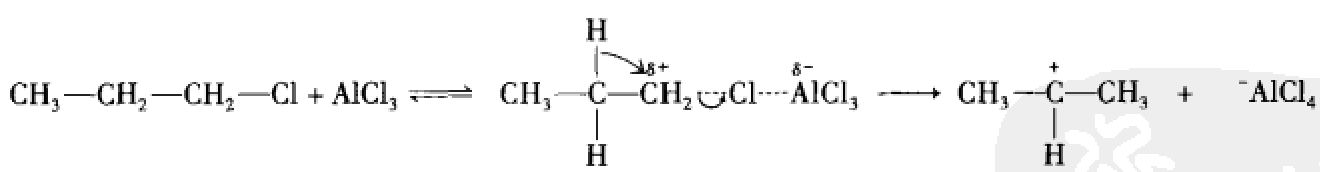
The BF_3 used in this reaction is consumed and not regenerated. A full equivalent of the Lewis acid is needed, so we say that the reaction is *promoted* by BF_3 rather than *catalyzed* by BF_3.

Limitations of the Friedel-Crafts Alkylation Although the Friedel-Crafts alkylation looks good in principle, it has three major limitations that severely restrict its use.

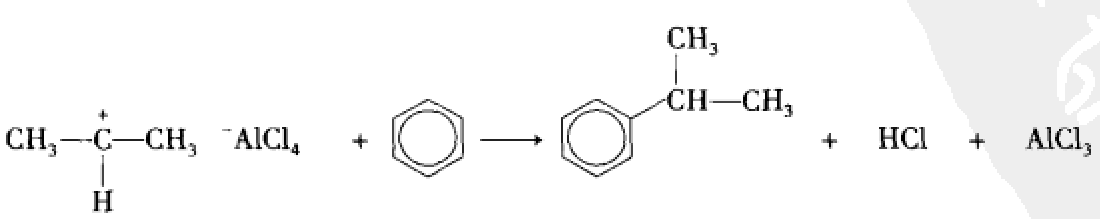
Limitation 1 Friedel-Crafts reactions work only with benzene, activated benzene derivatives, and halobenzenes. They fail with strongly deactivated systems such as nitrobenzene, benzenesulfonic acid, and phenyl ketones. In some cases, we can get around this limitation by adding the deactivating group or changing an activating group into a deactivating group *after* the Friedel-Crafts step.

Limitation 2 Like other carbocation reactions, the Friedel-Crafts alkylation is susceptible to carbocation rearrangements. As a result, only certain alkylbenzenes can be made using the Friedel-Crafts alkylation. *t*-Butylbenzene, isopropylbenzene, and ethylbenzene can be synthesized using the Friedel-Crafts alkylation because the corresponding cations are not prone to rearrangement. Consider what happens, however, when we try to make *n*-propylbenzene by the Friedel-Crafts alkylation.

Ionization with rearrangement gives isopropyl cation

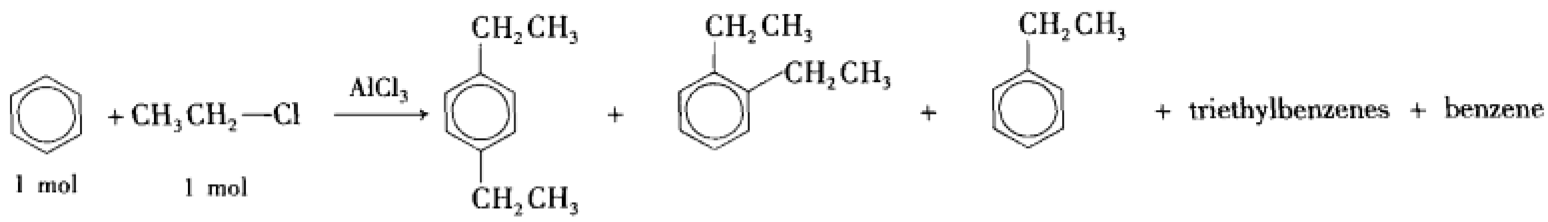


Reaction with benzene gives isopropylbenzene



Limitation 3 Because alkyl groups are activating substituents, the product of the Friedel-Crafts alkylation is *more reactive* than the starting material. Multiple alkylations are hard to avoid. This limitation can be severe. If we need to make ethylbenzene, we might try adding some $AlCl_3$ to a mixture of 1 mol of ethyl chloride and 1 mol of benzene. As some ethylbenzene is formed, however, it is activated, reacting even faster than benzene itself.

The product is a mixture of some (ortho and para) diethylbenzenes, some triethylbenzenes, a small amount of ethylbenzene, and some leftover benzene.



The problem of overalkylation can be avoided by using a large excess of benzene. For example, if 1 mol of ethyl chloride is used with 50 mol of benzene, the concentration of ethylbenzene is always low, and the electrophile is more likely to react with benzene than with ethylbenzene. Distillation separates the product from excess benzene. This is a common industrial approach, since a continuous distillation can recycle the unreacted benzene.

In the laboratory, we must often alkylate aromatic compounds that are more expensive than benzene. Because we cannot afford to use a large excess of the starting material, a more selective method is needed. Fortunately, the Friedel-Crafts acylation, discussed in Section 18−11, introduces just one group without danger of polyalkylation or rearrangement.

PROBLEM 18−6

Predict the products (if any) of the following reactions.

(**a**) (excess) benzene + isobutyl chloride + $AlCl_3$

(**b**) (excess) toluene + 1-butanol + BF_3

(**c**) (excess) nitrobenzene + 2-chloropropane + $AlCl_3$

(**d**) (excess) benzene + 3,3-dimethyl-1-butene + HF

PROBLEM 18−7

Which reactions will produce the desired product in good yield? You may assume that aluminum chloride is added as a catalyst in each case. For the reactions that will not give a good yield of the desired product, predict the major products.

Reagents	Desired Product
(**a**) benzene + *n*-butyl bromide	*n*-butylbenzene
(**b**) ethylbenzene + *t*-butyl chloride	*p*-ethyl-*t*-butylbenzene
(**c**) bromobenzene + ethyl chloride	*p*-bromoethylbenzene
(**d**) ethylbenzene + bromine	*p*-bromoethylbenzene
(**e**) anisole + methyl iodide (3 mol)	2,4,6-trimethylanisole

PROBLEM 18−8

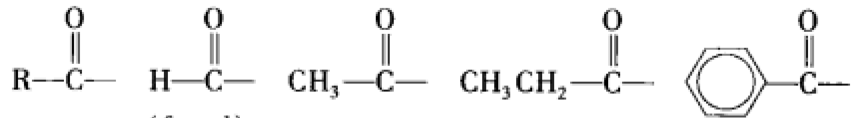
Show how you would synthesize the following aromatic derivatives from benzene.

(**a**) *p*-*t*-butylnitrobenzene (**b**) *p*-toluenesulfonic acid (**c**) *p*-chlorotoluene

18−11 The Friedel-Crafts Acylation

An **acyl group** is a carbonyl group with an alkyl group attached. Acyl groups are named systematically by drop-

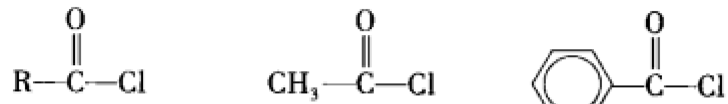
ping the final *-e* from the alkane name and adding the *-oyl* suffix. Historical names are often used for the *formyl group*, the *acetyl group*, and the *propionyl group*, however.



(formyl) (acetyl) (propionyl)

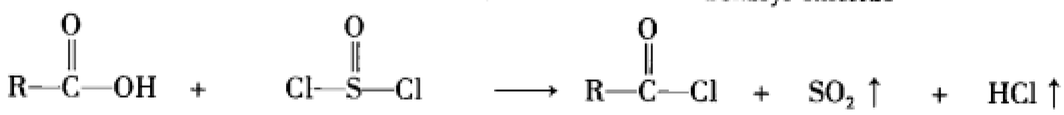
acyl group methanoyl ethanoyl propanoyl benzoyl

An **acyl chloride** is an acyl group bonded to a chlorine atom. Acyl chlorides are made by reaction of the corresponding carboxylic acids with thionyl chloride. Therefore, acyl chlorides are also called **acid chlorides**.



(an acid chloride)

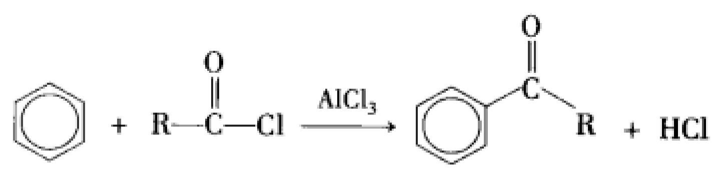
an acyl chloride acetyl chloride benzoyl chloride



a carboxylic acid thionyl chloride (二氯亚砜,亚硫酰氯) an acyl chloride (酰氯)

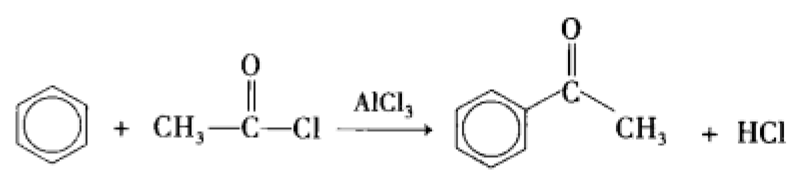
In the presence of aluminum chloride, an acyl chloride reacts with benzene (or an activated benzene derivative) to give a phenyl ketone: an *acylbenzene*. The **Friedel-Crafts acylation** is analogous to the Friedel-Crafts alkylation, except that the reagent is an acyl chloride instead of an alkyl halide and the product is an acylbenzene (a "phenone") instead of an alkylbenzene.

Friedel-Crafts acylation



benzene acyl halide (酰卤) an acylbenzene (a phenyl ketone)

Example



benzene acetyl chloride (乙酰氯) acetylbenzene (95%) (acetophenone)

18-11A Mechanism of Acylation

The mechanism of Friedel-Crafts acylation (shown next) resembles that for alkylation, except that the carbonyl group helps to stabilize the cationic intermediate. The acyl halide forms a complex with aluminum chloride; loss of the tetrachloroaluminate ion ($^-AlCl_4$) gives a resonance-stabilized **acylium ion.** The acylium ion is a strong electrophile. It reacts with benzene or an activated benzene derivative to form an acylbenzene.

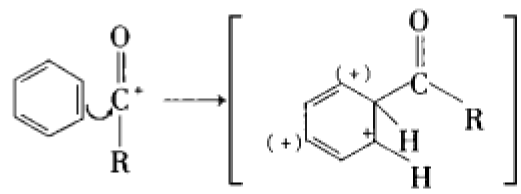
MECHANISM 18-6 Friedel-Crafts Acylation

Friedel-Crafts acylation is an electrophilic aromatic substitution with an acylium ion acting as the electrophile.

***Step 1*:** Formation of an acylium ion.

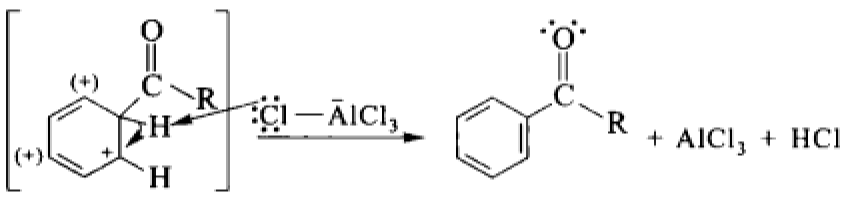
acyl chloride complex acylium ion（酰基离子）

Step 2：Electrophilic attack forms a sigma complex.



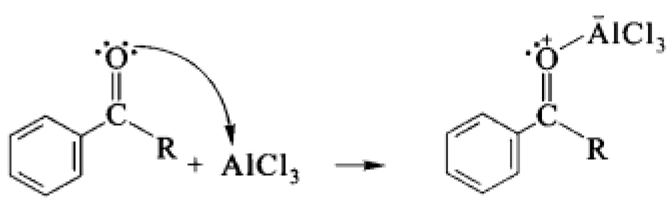
sigma complex

Step 3：Loss of a proton regenerates the aromatic system.



sigma complex acylbenzene

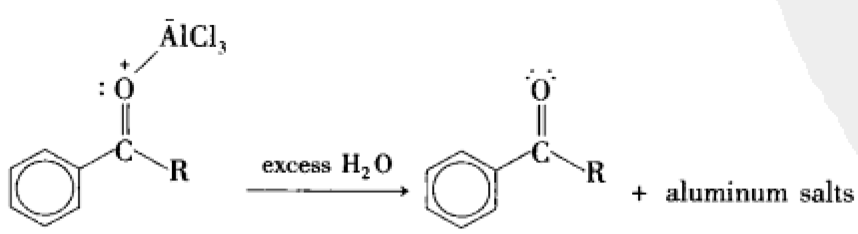
Step 4：Complexation of the product.



acylbenzene product complex

The product complex must be hydrolyzed (by water) to release the free acylbenzene.

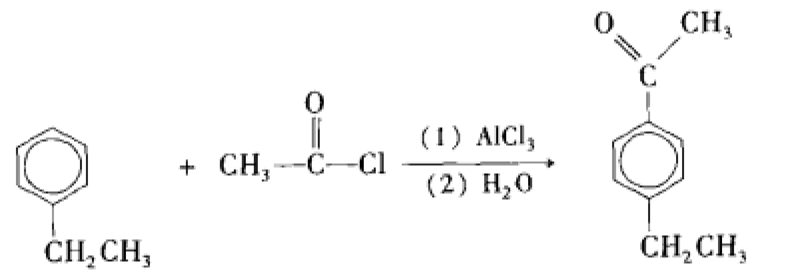
The product of acylation (the acylbenzene) is a ketone. The ketone's carbonyl group has nonbonding electrons that complex with the Lewis acid ($AlCl_3$), requiring a full equivalent of $AlCl_3$ in the acylation. The initial product is the aluminum chloride complex of the acylbenzene. Addition of water hydrolyzes this complex, giving the free acylbenzene.



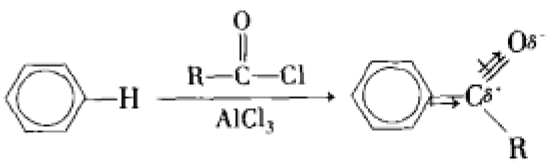
product complex free acylbenzene

The electrophile in the Friedel-Crafts acylation appears to be a large, bulky complex, such as $R-\overset{+}{C}=O\ ^{-}AlCl_4$. Para substitution usually prevails when the aromatic substrate has an ortho, para-directing

group, possibly because the electrophile is too bulky for effective attack at the ortho position. For example, when ethylbenzene reacts with acetyl chloride, the major product is *p*-ethylacetophenone.



One of the most attractive features of the Friedel-Crafts acylation is the deactivation of the product toward further substitution. The acylbenzene has a carbonyl group (a deactivating group) bonded to the aromatic ring. Since Friedel-Crafts reactions do not occur on strongly deactivated rings, the acylation stops after one substitution.



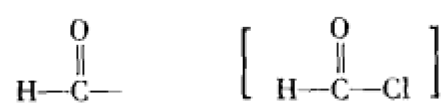
Thus, Friedel-Crafts acylation overcomes two of the three limitations of the alkylation: The acylium ion is resonance-stabilized, so that no rearrangements occur; and the acylbenzene product is deactivated, so that no further reaction occurs. Like the alkylation, however, the acylation fails with strongly deactivated aromatic rings.

SUMMARY Comparison of Friedel-Crafts Alkylation and Acylation

Alkylation	Acylation
The alkylation cannot be used with strongly deactivated derivatives.	Also true: Only benzene, halobenzenes, and activated derivatives are suitable.
The carbocations involved in the alkylation may rearrange.	Resonance-stabilized acylium ions are not prone to rearrangement.
Polyalkylation is commonly a problem.	The acylation forms a deactivated acylbenzene, which does not react further.

18-11B The Gatterman-Koch Formylation: Synthesis of Benzaldehydes

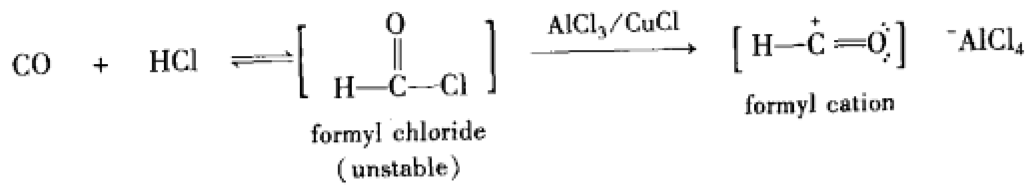
We cannot add a formyl group to benzene by Friedel-Crafts acylation in the usual manner. The problem lies with the necessary reagent, formyl chloride, which is unstable and cannot be bought or stored.

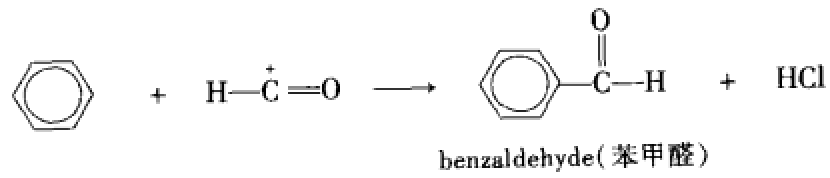


formyl group (甲酰基)　　formyl chloride (甲酰氯)

Formylation can be accomplished by using a high-pressure mixture of carbon monoxide and HCl together with a catalyst consisting of a mixture of cuprous chloride (CuCl) and aluminum chloride. This mixture generates the formyl cation, possibly through a small concentration of formyl chloride. The reaction with benzene gives formylbenzene, better known as benzaldehyde. This reaction, called the **Gatterman-Koch synthesis**, is widely used

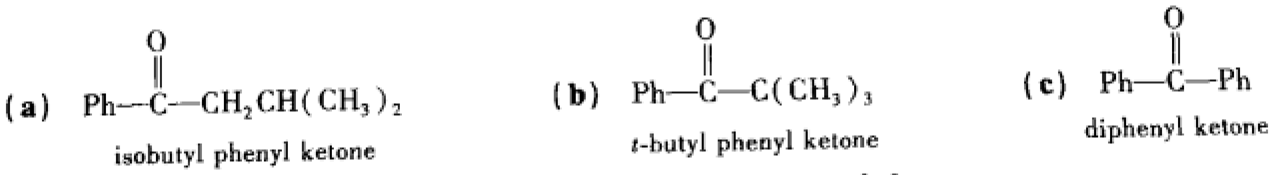
in industry to synthesize aryl aldehydes.





PROBLEM 18-9

Show how you would use the Friedel-Crafts acylation, Clemmensen reduction, and/or Gatterman-Koch synthesis to prepare the following compounds:

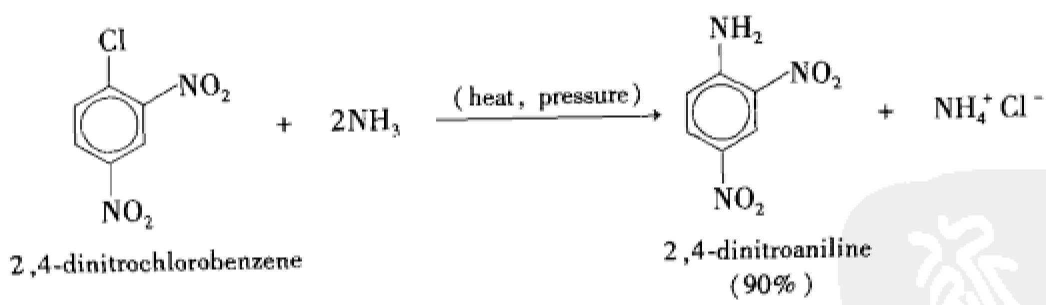


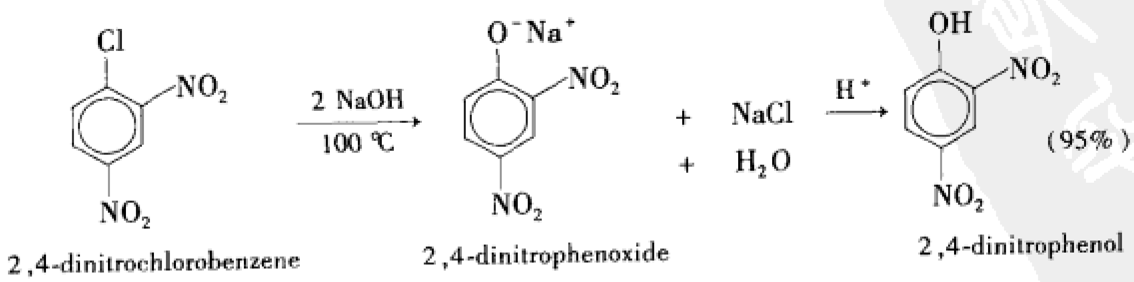
(d) *p*-methoxybenzaldehyde **(e)** 1-phenyl-2,2-dimethylpropane

(f) *n*-butylbenzene

18-12 Nucleophilic Aromatic Substitution

Nucleophiles can displace halide ions from aryl halides, particularly if there are strong electron-withdrawing groups ortho or para to the halide. Because a nucleophile substitutes for a leaving group on an aromatic ring, this class of reactions is called **nucleophilic aromatic substitution**. The following examples show that both ammonia and hydroxide ion can displace chloride from 2,4-dinitrochlorobenzene:





Electrophilic aromatic substitution is the most important reaction of aromatic compounds because it has broad applications for a wide variety of aromatic compounds. In contrast, *nucleophilic* aromatic substitution has restricted applications. In nucleophilic aromatic substitution, a strong nucleophile replaces a leaving group, such as a halide. What is the mechanism of nucleophilic aromatic substitution? It cannot be the S_N2 mechanism because aryl halides cannot achieve the correct geometry for back-side displacement. The aromatic ring blocks approach of the nucleophile to the back of the carbon bearing the halogen.

The S_N1 mechanism cannot be involved either. Strong nucleophiles are required for nucleophilic aromatic substitution, and the reaction rate is proportional to the concentration of the nucleophile. Thus, the nucleophile must be involved in the transition state.

Electron-withdrawing substituents (such as nitro groups) *activate* the ring toward nucleophilic aromatic substitution, suggesting that the transition state is developing a negative charge on the ring. In fact, nucleophilic aromatic substitutions are difficult without at least one powerful electron-withdrawing group. (This effect is the opposite of that for *electrophilic* aromatic substitution, where electron-withdrawing substituents slow or stop the reaction.)

Nucleophilic aromatic substitutions have been studied in detail. Either of two mechanisms may be involved, depending on the reactants. One mechanism is similar to the electrophilic aromatic substitution mechanism, except that nucleophiles and carbanions are involved rather than electrophiles and carbocations. The other mechanism involves "benzyne," an interesting and unusual reactive intermediate.

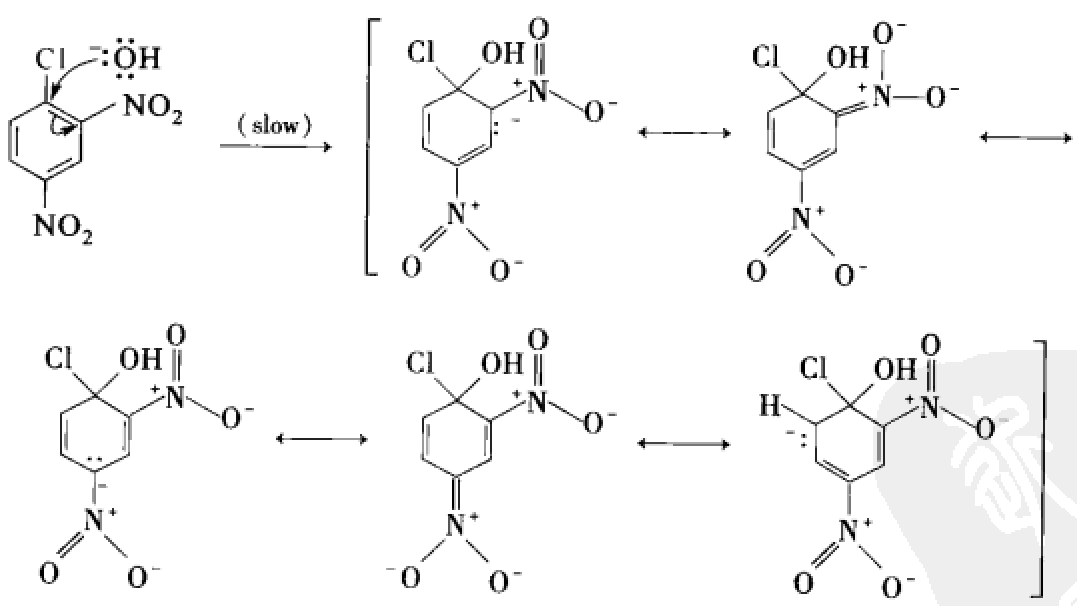
18-12A The Addition-Elimination Mechanism

Consider the reaction of 2,4-dinitrochlorobenzene with sodium hydroxide (shown next). When hydroxide (the nucleophile) attacks the carbon bearing the chlorine, a negatively charged sigma complex results. The negative charge is delocalized over the ortho and para carbons of the ring and further delocalized into the electron-withdrawing nitro groups. Loss of chloride from the sigma complex gives 2,4-dinitrophenol, which is deprotonated in this basic solution.

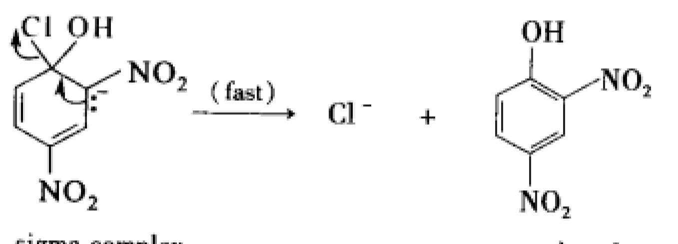
KEY MECHANISM 18-7 Nucleophilic Aromatic Substitution (Addition-Elimination)

The addition-elimination mechanism requires strong electron-withdrawing groups to stabilize a negatively charged sigma complex.

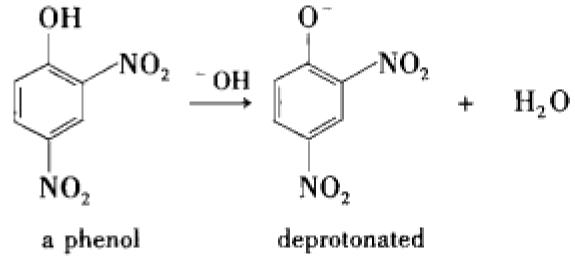
Step 1: Attack by the nucleophile gives a resonance-stabilized sigma complex.



Step 2: Loss of the leaving group gives the product.

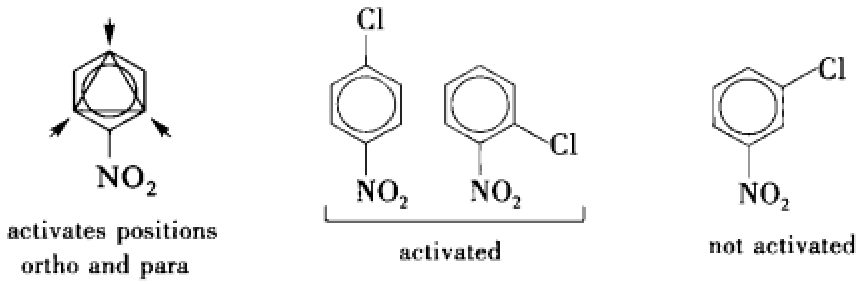


***Step 3*:** This product (a phenol) is acidic, and is deprotonated by the base.



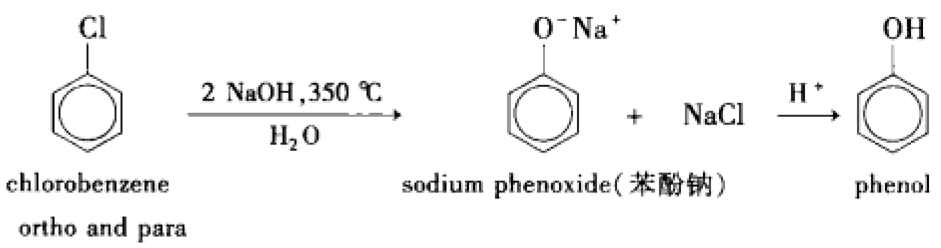
After the reaction is complete, acid would be added to reprotonate the phenol.

The resonance forms shown in the mechanism box illustrate how nitro groups ortho and pare to the halogen help to stabilize the intermediate (and the transition state leading to it). Without strong electron-withdrawing groups in these positions, formation of the negatively charged sigma complex is unlikely.



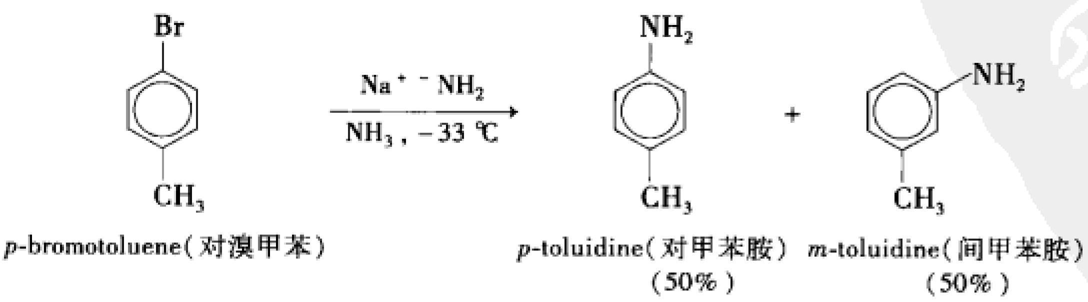
18-12B The Benzyne Mechanism: Elimination-Addition

The addition-elimination mechanism for nucleophilic aromatic substitution requires strong electron-withdrawing substituents on the aromatic ring. Under extreme conditions, however, unactivated halobenzenes react with strong bases. For example, a commercial synthesis of phenol (the "Dow process") involves treatment of chlorobenzene with sodium hydroxide and a small amount of water in a pressurized reactor at 350 ℃:



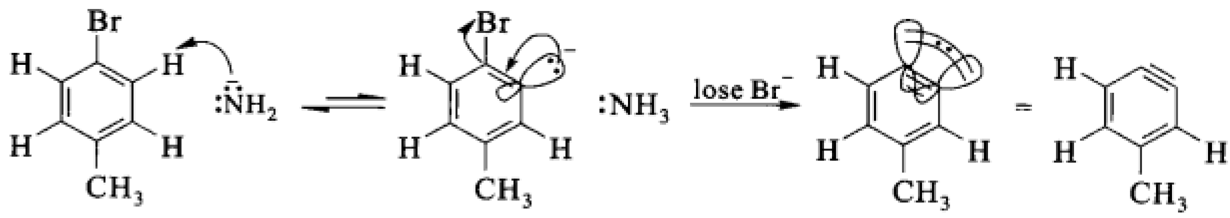
Similarly, chlorobenzene reacts with sodium amide ($NaNH_2$, an extremely strong base) to give aniline, Ph—NH_2. This reaction does not require high temperatures, taking place in liquid ammonia at −33 ℃.

Nucleophilic substitution of unactivated benzene derivatives occurs by a mechanism different from the addition-elimination we saw with the nitrosubstituted halobenzenes. A clue to the mechanism is provided by the reaction of *p*-bromotoluene with sodium amide. The products are a 50:50 mixture of *m*- and *p*-toluidine.



These two products can be explained by an elimination-addition mechanism, called the **benzyne mechanism** because of the unusual intermediate. Sodium amide (or sodium hydroxide in the Dow process) reacts as a *base*,

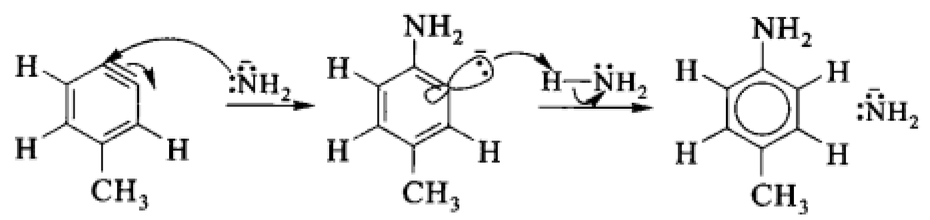
abstracting a proton. The product is a carbanion with a negative charge and a nonbonding pair of electrons localized in the sp^2 orbital that once formed the C—H bond.



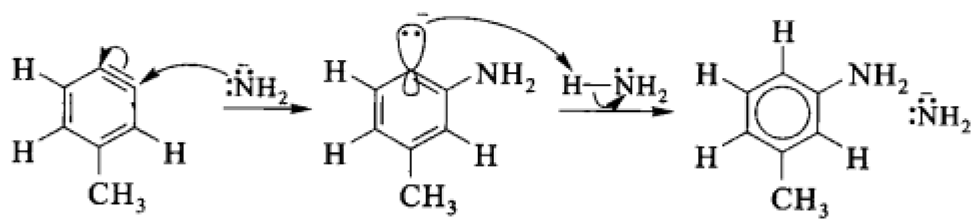
carbanion(碳负离子) a"benzyne"(苯炔)

The carbanion can expel bromide ion to become a neutral species. As bromide leaves with its bonding electrons, an empty sp^2 orbital remains. This orbital overlaps with the filled orbital adjacent to it, giving additional bonding between these two carbon atoms. The two sp^2 orbitals are directed 60° away from each other, so their overlap is not very effective. This reactive intermediate is called a **benzyne** because it can be symbolized by drawing a triple bond between these two carbon atoms. Triple bonds are usually linear, however, so this is a very reactive, highly strained triple bond.

Amide ion is a strong nucleophile, attacking at either end of the weak, reactive benzyne triple bond. Subsequent protonation gives toluidine. About half of the product results from attack by the amide ion at the meta carbon, and about half from attack at the para carbon.



benzyne carbanion *p*-toluidine



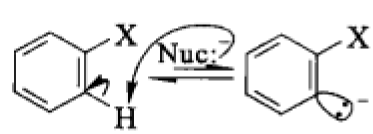
benzyne carbanion *m*-toluidine

In summary, the benzyne mechanism operates when the halobenzene is unactivated toward nucleophilic aromatic substitution, and forcing conditions are used with a strong base. A two-step elimination forms a reactive benzyne intermediate. Nucleophilic attack, followed by protonation, gives the substituted product.

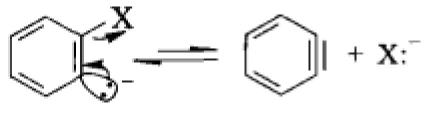
MECHANISM 18-8 Nucleophilic Aromatic Substitution (Benzyne Mechanism)

The benzyne mechanism (elimination-addition) is likely when the ring has no strong electron-withdrawing groups. It usually requires a powerful base or high temperatures.

Step 1: Deprotonation adjacent to the leaving group gives a carbanion.

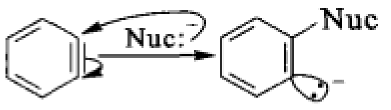


***Step 2*:** The carbanion expels the leaving group to give a "benzyne" intermediate.



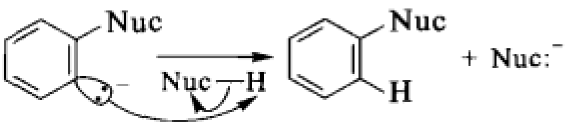
"benzyne" (苯炔)

***Step 3*:** The nucleophile attacks at either end of the reactive benzyne triple bond.



"benzyne"

***Step 4*:** Reprotonation gives the product.



PROBLEM 18-10

Propose a mechanism that shows why *p*-chlorotoluene reacts with sodium hydroxide at 350 ℃ to give a mixture of *p*-cresol and *m*-cresol.

PROBLEM 18-11

Propose mechanisms and show the expected products of the following reactions.

(a) 2,4-dinitrochlorobenzene + sodium methoxide ($NaOCH_3$)

(b) 2,4-dimethylchlorobenzene + sodium hydroxide, 100 ℃

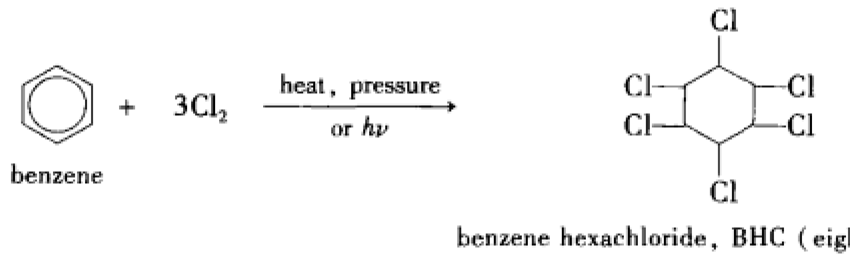
(c) *p*-nitrobromobenzene + methylamine ($CH_3—NH_2$)

(d) 2,4-dinitrochlorobenzene + excess hydrazine ($H_2N—NH_2$)

18-13 Addition Reactions of Benzene Derivatives

18-13A Chlorination

Although substitution is more common, aromatic compounds may undergo addition if forcing conditions are used. When benzene is treated with an excess of chlorine under heat and pressure (or with irradiation by light), six chlorine atoms add to form 1,2,3,4,5,6-hexachlorocyclohexane. This product is often called *benzene hexachloride* (BHC) because it is synthesized by direct chlorination of benzene.



benzene

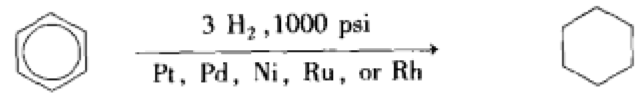
benzene hexachloride, BHC (eight isomers)
(六氯化苯)

The addition of chlorine to benzene, believed to involve a free-radical mechanism, is normally impossible to

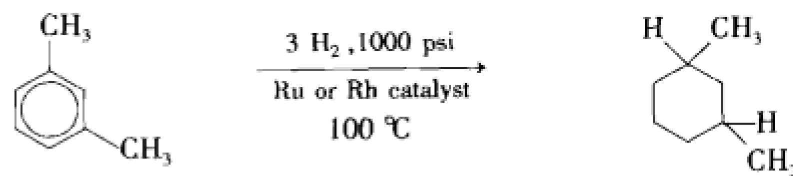
stop at an intermediate stage. The first addition destroys the ring's aromaticity, and the next 2 mol of Cl_2 add very rapidly. All eight possible stereoisomers are produced in various amounts. The most important isomer for commercial purposes is the insecticide *lindane*, which is used in a shampoo to kill head lice.

18−13B Catalytic Hydrogenation of Aromatic Rings

Catalytic hydrogenation of benzene to cyclohexane takes place at elevated temperatures and pressures, often catalyzed by ruthenium or rhodium. Substituted benzenes react to give substituted cyclohexanes; disubsituted benzenes usually give mixtures of cis and trans isomers.



benzene cyclohexane (100%)

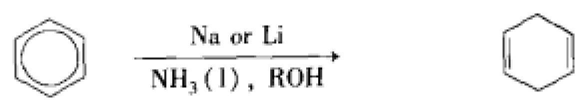


m-xylene (间二甲苯) 1,3-dimethylcyclohexane (100%) (mixture of cis and trans)

Catalytic hydrogenation of benzene is the commercial method for producing cyclohexane and substituted cyclohexane derivatives. The reduction cannot be stopped at an intermediate stage (cyclohexene or cyclohexadiene) because these alkenes are reduced faster than benzene.

18−13C Birch Reduction

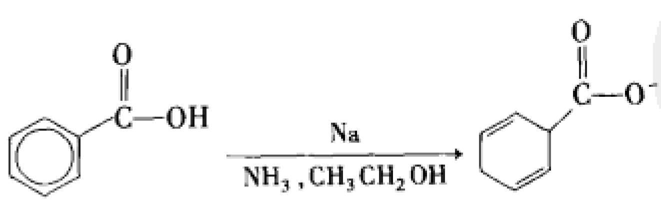
In 1944, the Australian chemist A. J. Birch found that benzene derivatives are reduced to nonconjugated 1,4-cyclohexadienes by treatment with sodium or lithium in a mixture of liquid ammonia and an alcohol. The **Birch reduction** provides a convenient method for making a wide variety of interesting and useful cyclic dienes.



benzene 1,4-cyclohexadiene (90%)

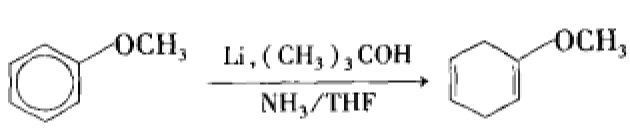
The Birch reduction takes place on carbon atoms bearing electron-withdrawing substituents (such as those containing carbonyl groups) and not on carbon atoms bearing electron-releasing substituents (such as alkyl and alkoxyl groups).

A carbon bearing an electron-withdrawing carbonyl group is reduced



(90%)

A carbon bearing an electron-releasing alkoxyl group is not reduced



(85%)

Substituents that are strongly electron-releasing (—OCH_3 for example) deactivate the aromatic ring toward Birch reduction. Lithium is often used with these deactivated systems, together with a cosolvent (often THF)

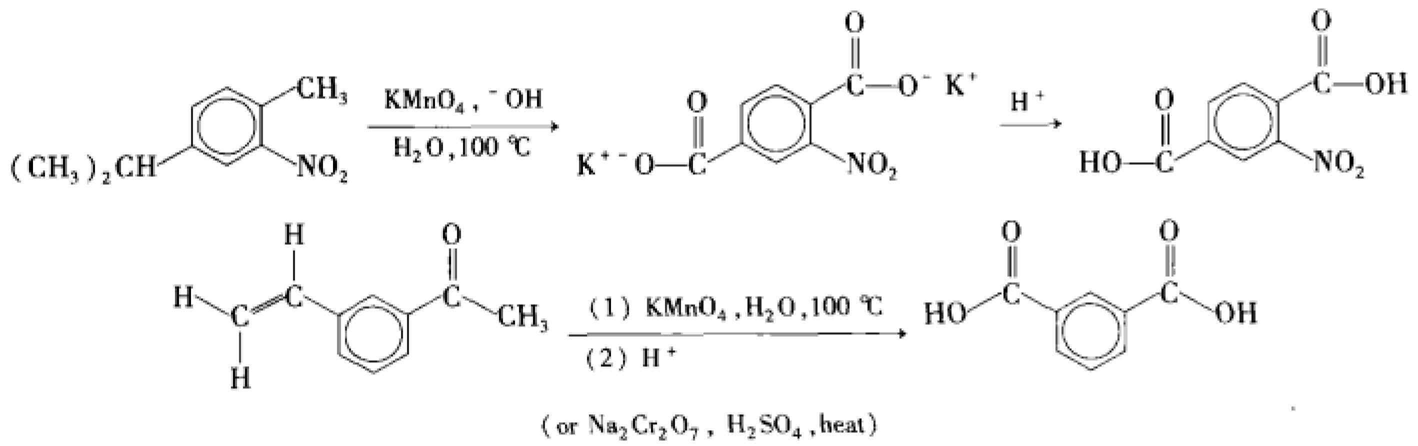
and a weaker proton source (t-butyl alcohol). The stronger reducing agent, combined with a weaker proton source, enhances the reduction.

18−14 Side-Chain Reactions of Benzene Derivatives

Many reactions are not affected by the presence of a nearby benzene ring; yet others depend on the aromatic ring to promote the reaction. For example, the Clemmensen reduction is occasionally used to reduce aliphatic ketones to alkanes, but it works best reducing aryl ketones to alkylbenzenes. Several additional side-chain reactions show the effects of a nearby aromatic ring.

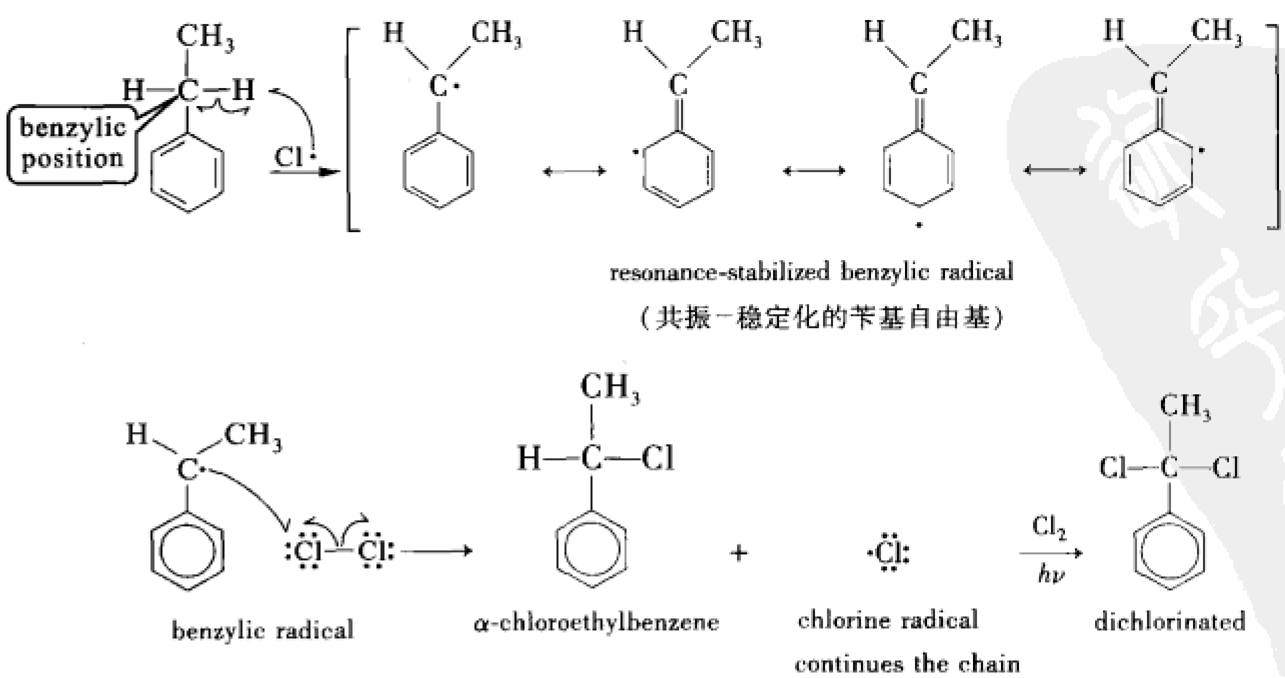
18−14A Permanganate Oxidation

An aromatic ring imparts extra stability to the nearest carbon atom of its side chains. The aromatic ring and *one* carbon atom of a side chain can survive a vigorous permanganate oxidation. The product is a carboxylate salt of benzoic acid. This oxidation is occasionally useful for making benzoic acid derivatives, as long as any other functional groups are resistant to oxidation. (Hot chromic acid can also be used for this oxidation.)

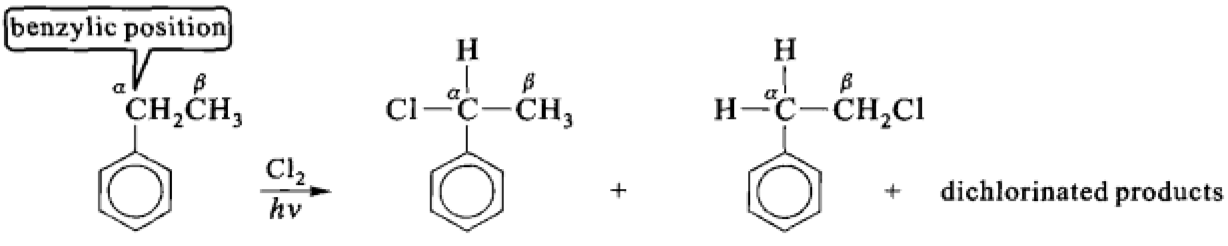


18−14B Side-Chain Halogenation

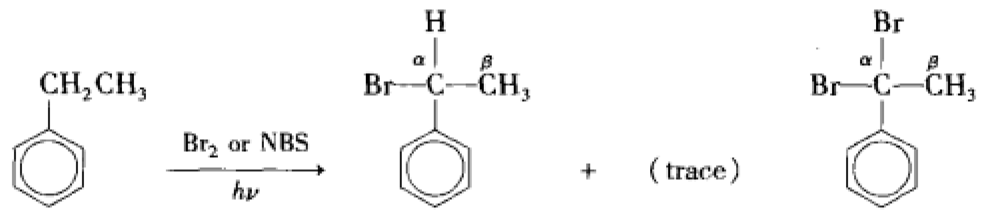
Alkylbenzenes undergo free-radical halogenation much more easily than alkanes because abstraction of a hydrogen atom at a **benzylic position** gives a resonance-stabilized benzylic radical. For example, ethylbenzene reacts with chlorine in the presence of light to give α-chloroethylbenzene. Further chlorination can occur to give a dichlorinated product.



Although chlorination shows a preference for α substitution (the α position is the benzylic carbon bonded to the benzene ring), the chlorine radical is too reactive to give entirely benzylic substitution. Mixtures of isomers are often produced. In the chlorination of ethylbenzene, for example, there is a significant amount of substitution at the β carbon.



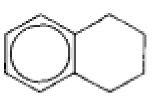
Bromine radicals are not as reactive as chlorine radicals, so bromination is more selective than chlorination. Bromine reacts exclusively at the benzylic position.



Either elemental bromine (much cheaper) or *N*-bromosuccinimide may be used as the reagent for benzylic bromination. *N*-Bromosuccinimide is preferred for allylic bromination because Br_2 can add to the double bond. This is not a problem with the relatively unreactive benzene ring unless it has powerful activating substituents.

PROBLEM 18-12

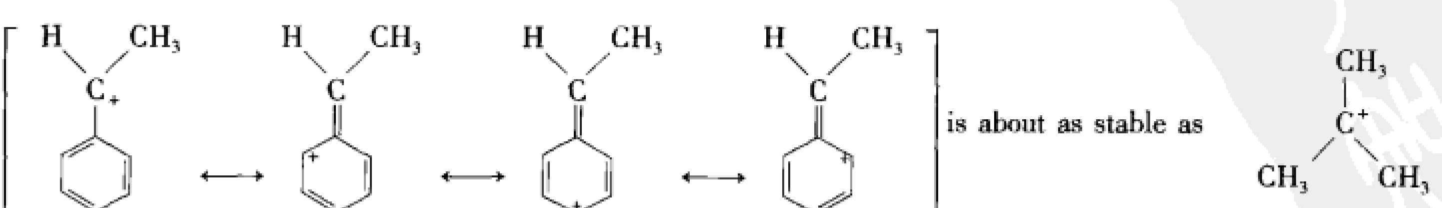
Predict the major products when the following compounds are irradiated by light and treated with (1) 1 mol of Br_2 and (2) excess Br_2.

(a) isopropylbenzene **(b)**  (tetralin)

18-14C Nucleophilic Substitution at the Benzylic Position

In Chapter 11, we saw that allylic halides are more reactive than most alkyl halides in both S_N1 and S_N2 reactions. Benzylic halides are also more reactive in these substitutions, for reasons similar to those for allylic halides.

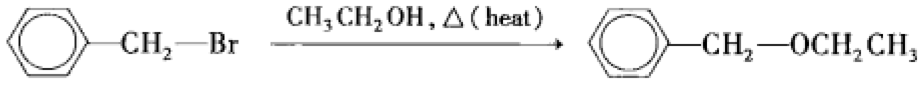
First-Order Reactions First-order nucleophilic substitution requires ionization of the halide to give a carbocation. In the case of a benzylic halide, the carbocation is resonance-stabilized. For example, the 1-phenylethyl cation (2°) is about as stable as a 3° alkyl cation.



1-phenylethyl cation (2°)
(1-苯基乙基碳正离子)

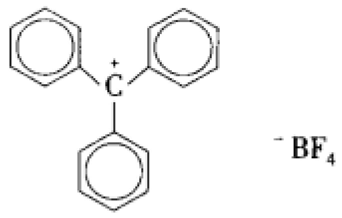
t-butyl cation (3°)
(叔丁基碳正离子)

Because they form relatively stable carbocations, benzyl halides undergo S_N1 reactions more easily than do most alkyl halides.



benzyl bromide(苄基溴) benzyl ethyl ether(苄基乙基醚)

If a benzylic cation is bonded to more than one phenyl group, the stabilizing effects are additive. An extreme example is the triphenylmethyl cation. This cation is exceptionally stable, with three phenyl groups to stabilize the positive charge. In fact, triphenylmethyl fluoroborate can be stored for years as a stable ionic solid.



triphenylmethyl fluoroborate(甲基三苯基四氟硼)

Second-Order Reactions Like allylic halides, benzylic halides are about 100 times more reactive than primary alkyl halides in S_N2 displacement reactions. The explanation for this enhanced reactivity is similar to that for the reactivity of allylic halides.

During S_N2 displacement on a benzylic halide, the *p* orbital that partially bonds with the nucleophile and the leaving group also overlaps with the pi electrons of the ring (Figure 18-4). This stabilizing conjugation lowers the energy of the transition state, increasing the reaction rate.

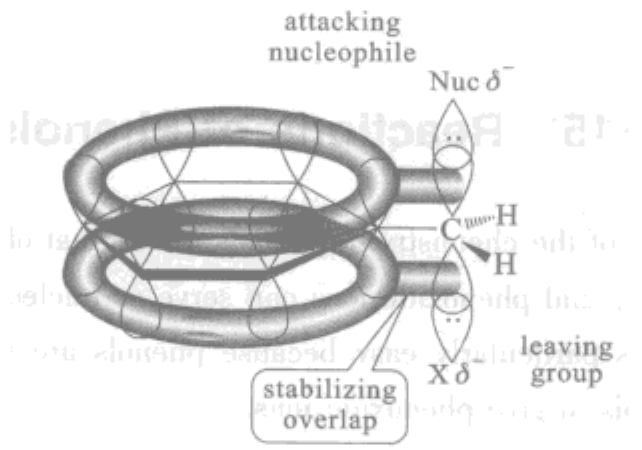
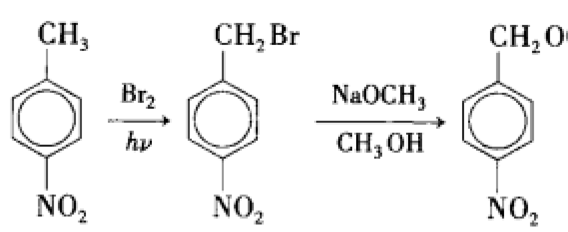
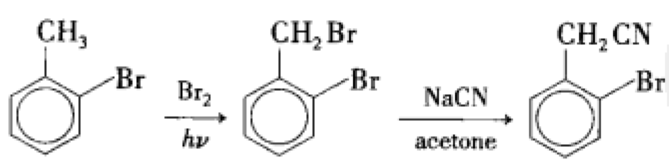


Figure 18-4 The transition state for S_N2 displacement of a benzylic halide is stabilized by conjugation with the pielectrons in the ring.

S_N2 reactions of benzyl halides efficiently convert aromatic methyl groups to functional groups. Halogenation, followed by substitution, gives the functionalized product.





PROBLEM 18-13

(a) Based on what you know about the relative stabilities of alkyl cations and benzylic cations, predict the product of addition of HBr to 1-phenylpropene.

(b) Propose a mechanism for this reaction.

PROBLEM 18-14

(a) Based on what you know about the relative stabilities of alkyl radicals and benzylic radicals, predict the product of addition

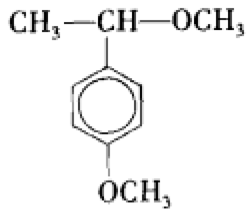
of HBr to 1-phenylpropene in the presence of a free-radical initiator.

(b) Propose a mechanism for this reaction.

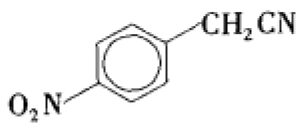
PROBLEM 18-15

Show how you would synthesize the following compounds, using the indicated starting materials.

(a) 3-phenyl-1-butanol from styrene

(b) 

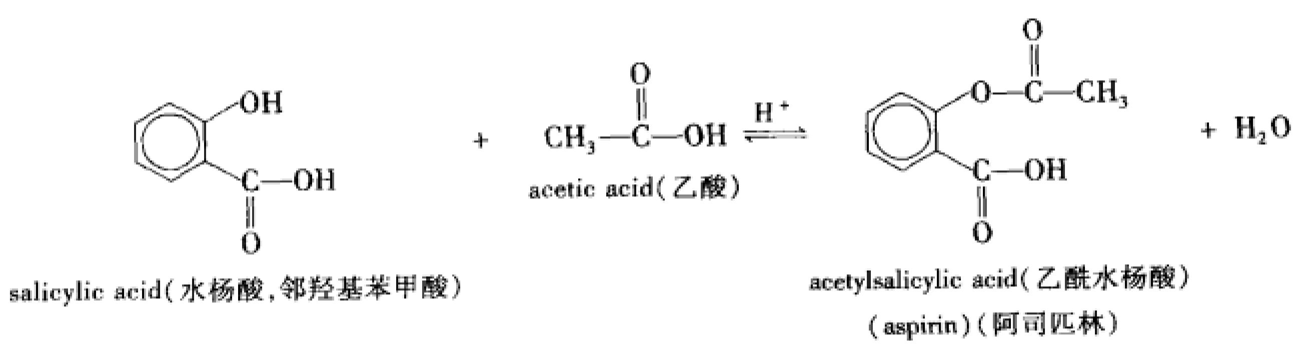
from anisole

(c) 

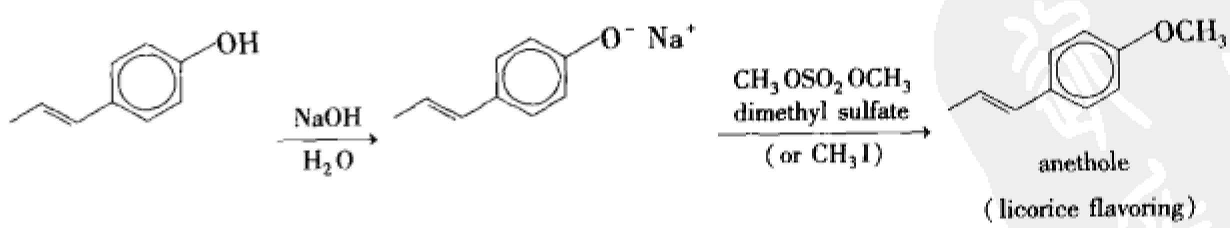
from toluene

18-15 Reactions of Phenols

Much of the chemistry of phenols is like that of aliphatic alcohols. For example, phenols can be acylated to give esters, and phenoxide ions can serve as nucleophiles in the Williamson ether synthesis. Formation of phenoxide ions is particularly easy because phenols are more acidic than water; aqueous sodium hydroxide deprotonates phenols to give phenoxide ions.



Aspirin inactivates two cyclooxygenases, named COX-1 and COX-2, and prevents the formation of critical prostaglandins in the body. Inhibition of COX-2 relieves the pain, while inhibition of COX-1 results in stomach irritation and upset.

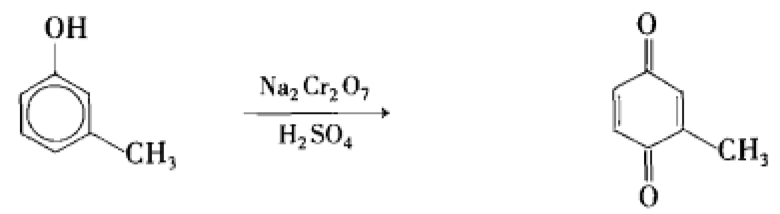


All the alcohol-like reactions shown involve breaking of the phenolic O—H bond. This is a common way for phenols to react. It is far more difficult to break the C—O bond of a phenol, however. Most alcohol reactions in which the C—O bond breaks are not possible with phenols. For example, phenols do not undergo acidcatalyzed elimination or S_N2 back-side attack.

Phenols also undergo reactions that are not possible with aliphatic alcohols. Let's consider some reactions that are peculiar to phenols.

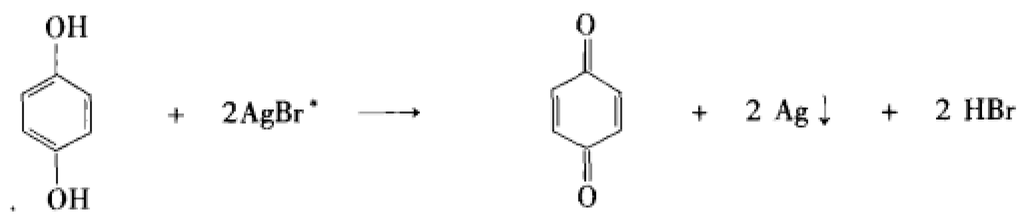
18-15A Oxidation of Phenols to Quinones

Phenols undergo oxidation, but they give different types of products from those seen with aliphatic alcohols. Chromic acid oxidation of a phenol gives a conjugated 1, 4-diketone called a **quinone**. In the presence of air, many phenols slowly autoxidize to dark mixtures containing quinones.



m-cresol [间甲(苯)酚] 2-methyl-1,4-benzoquinone (2-甲基-1,4-苯醌)

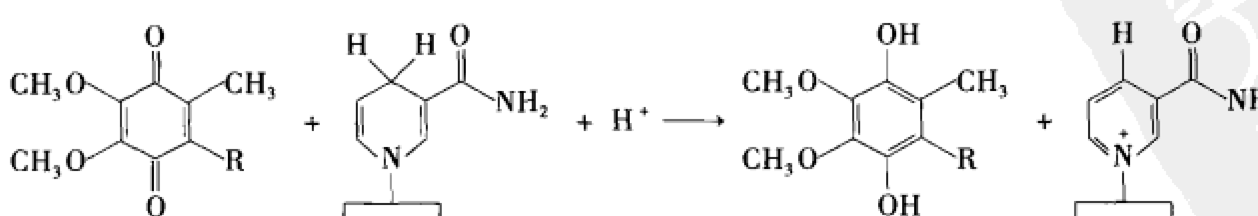
Hydroquinone (1,4-benzenediol) is easily oxidized because it already has two oxygen atoms bonded to the ring. Even very weak oxidants like silver bromide (AgBr) can oxidize hydroquinone. Silver bromide is reduced to black metallic silver in a light-sensitive reaction: Any grains of silver bromide that have been exposed to light ($AgBr^*$) react faster than unexposed grains.



hydroquinone(氢醌) (1,4-benzenediol)(1,4-苯二酚) quinone(醌) (1,4-benzoquinone)(1,4-苯醌)

Black-and-white photography is based on this reaction. A film containing small grains of silver bromide is exposed by a focused image. Where light strikes the film, the grains are activated. The film is then treated with a hydroquinone solution (the *developer*) to reduce the activated silver bromide grains, leaving black silver deposits where the film was exposed to light. The result is a negative image, with dark areas where light struck the film.

Quinones occur widely in nature, where they serve as biological oxidation-reduction reagents. The quinone *coenzyme Q* (CoQ) is also called *ubiquinone* because it seems ubiquitous (found everywhere) in oxygen-consuming organisms. Coenzyme Q serves as an oxidizing agent within the mitochondria of cells. The following reaction shows the reduction of coenzyme Q by NADH (the reduced form of nicotinamide adenine dinucleotide), which becomes oxidized to NAD^+.

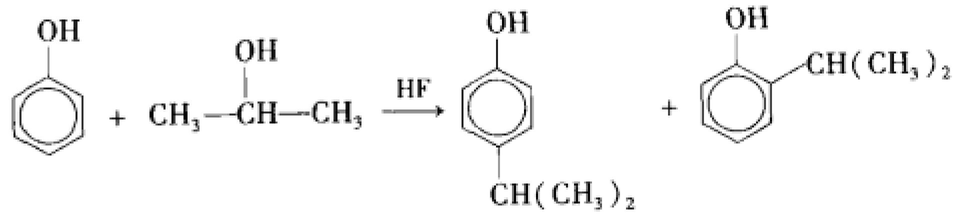


coenzyme Q(辅酶 Q) oxidized form; NADH reduced form; coenzyme Q reduced form; NAD^+ oxidized form

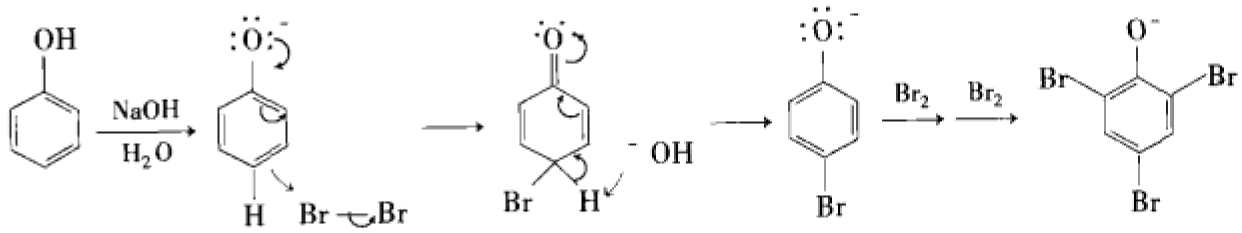
$$R = \left(CH_2-CH=\overset{CH_3}{\overset{|}{C}}-CH_2\right)_{10}H$$

18-15B Electrophilic Aromatic Substitution of Phenols

Phenols are highly reactive substrates for electrophilic aromatic substitution because the nonbonding electrons of the hydroxyl group stabilize the sigma complex formed by attack at the ortho or para position (Section 18-6B). Therefore, the hydroxyl group is strongly activating and ortho, para-directing. Phenols are excellent substrates for halogenation, nitration, sulfonation, and some Friedel-Crafts reactions. Because they are highly reactive, phenols are usually alkylated or acylated using relatively weak Friedel-Crafts catalysts (such as HF) to avoid overalkylation or overacylation.

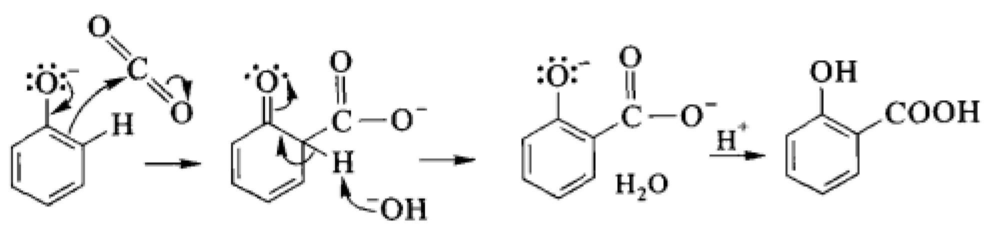


Phenoxide ions, easily generated by treating a phenol with sodium hydroxide, are even more reactive than phenols toward electrophilic aromatic substitution. Because they are negatively charged, phenoxide ions react with positively charged electrophiles to give neutral sigma complexes whose structures resemble quinones.



phenoxide ion sigma complex

Phenoxide ions are so strongly activated that they undergo electrophilic aromatic substitution with carbon dioxide, a weak electrophile. The carboxylation of phenoxide ion is an industrial synthesis of salicylic acid, which is then converted to aspirin.



salicylic acid(水杨酸)

PROBLEM 18-16

Predict the products formed when *m*-cresol (*m*-methylphenol) reacts with

(a) NaOH and then ethyl bromide
(b) acetyl chloride, $CH_3-\overset{O}{\overset{\|}{C}}-Cl$
(c) bromine in CCl_4 in the dark
(d) excess bromine in CCl_4 in the light
(e) sodium dichromate in H_2SO_4
(f) two equivalents of *t*-butyl chloride and $AlCl_3$

PROBLEM 18-17

Benzoquinone is a good Diels-Alder dienophile. Predict the products of its reaction with

(a) 1,3-butadiene (b) 1,3-cyclohexadiene (c) furan

PROBLEM 18-18

Phenol reacts with three equivalents of bromine in CCl_4 (in the dark) to give a product of formula $C_6H_3OBr_3$. When this product is added to bromine water, a yellow solid of molecular formula $C_6H_2OBr_4$ precipitates out of the solution. The IR spectrum of the yellow precipitate shows a strong absorption (much like that of a quinone) around 1680 cm^{-1}. Propose structures for the two products.

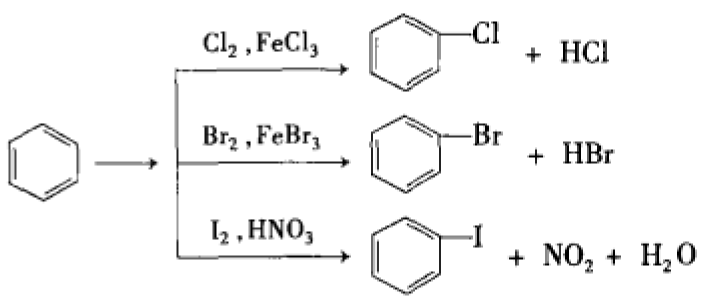
Summary in Chinese

本章概要

一、亲电芳香取代反应(electrophilic aromatic substitution)

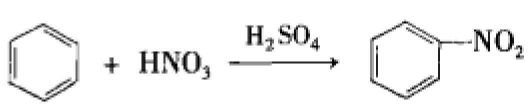
芳香烃化合物的主要性质是芳环上的亲电取代反应、氧化、还原反应及侧链的氧化、卤化反应。其中最重要的反应是亲电芳香取代反应,反应的决定速率步骤是亲电试剂与苯环的加成,生成离域的环己二烯正离子中间体,苯环失去芳香性。中间体快速脱质子恢复(取代的)苯环的芳香性,完成亲电取代反应。苯通过亲电取代反应可以制备烷基苯、酰基苯、卤代苯、硝基苯、苯磺酸等苯的衍生物。

1. 卤代反应(halogenation):



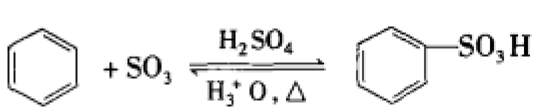
☆ FeX_3 是 Lewis 酸催化剂,有利于 X_2 发生异裂产生 X^+。HNO_3 的作用是将 I_2 氧化成 I^+。

2. 硝化反应(nitration):



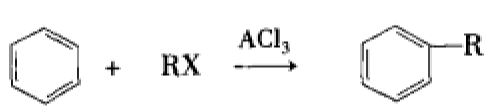
☆ H_2SO_4 的作用是使 HNO_3 产生亲电试剂 $^+NO_2$。

3. 磺化反应(sulfonation):



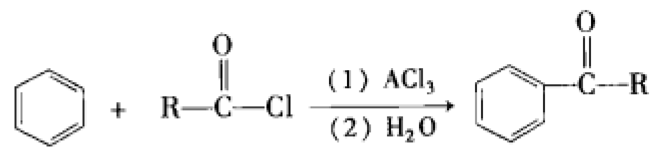
☆ 反应是可逆的;在合成上用于占位、导向作用。

4. 傅-克烷基化反应(Friedel-Crafts alkylation):



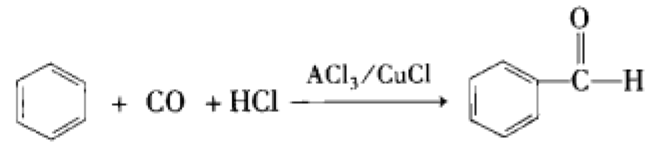
☆ 卤化物与催化剂形成的中间体碳正离子是亲电试剂,有烷基重排产物;容易生成多烷基产物;醇、烯烃也可作为烷基化试剂;苯环上有—NH_2 或—OH 基团时,由于它们可与 ACl_3 络合,从而影响反应的进行。

5. 傅-克酰基化反应(Friedel-Crafts acylation):



☆ 酰基碳正离子($R-\overset{O}{\overset{\|}{C}}{}^+$)是亲电试剂，不发生重排反应；不发生多酰基化反应；苯环上含有—NO_2 或—COOH 等吸电子基时，不发生此反应；苯环上带有—NH_2 或—OH 等基团时，它们与 ACl_3 络合，影响反应的进行；ACl_3 用量比烷基化反应大，因为酰基化产物中有羰基，能与 ACl_3 络合；酸酐也可作为酰基化试剂。

6. Gatterman-Koch 合成：



☆ 可用于合成苯甲醛，亲电试剂是[$HC^+=O$] $AlCl_4^-$ 。

二、取代基对亲电芳香取代反应活性和定位的影响

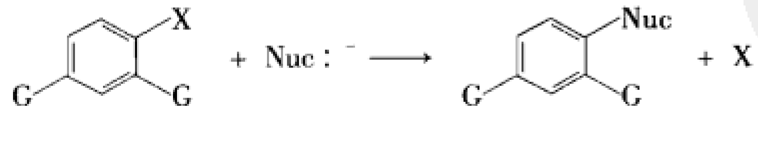
1. 取代苯的亲电取代反应活性：苯环上电子云密度越高，越有利于亲电试剂 E^+ 的进攻，反应活性越高。苯环上的取代基可以分成两类：一类是通过给电子活化苯环的活化基团，另一类是通过吸电子钝化苯环的钝化基团，吸电子或给电子的机理是基于诱导效应或共轭效应。这两种效应可以同时发挥作用，或相互增强或相互抵消。$-\ddot{O}:^-$、$-\ddot{N}R_2$、$-\ddot{O}H$、$-\ddot{O}R$、—R 等是活化基团；$-N^+R_3$、$-NO_2$、$-CF_3$、—CN、$-SO_3H$、$-\overset{O}{\overset{\|}{C}}-$ 、—X(卤素)是钝化基团。活化基团的特征是与苯环直接相连的原子上均有能与苯环发生共轭的孤对电子(—R 除外)；钝化基团的特征是与苯环直接相连的原子均显电正性(卤素除外)。

2. 单取代苯的定位效应：活化基团是邻对位定位基，连有活化基团的取代苯，亲电取代反应比苯快；钝化基团是间位定位基，连有钝化基团的取代苯，亲电取代反应比苯慢，卤素是例外，它是弱的钝化基团，却是邻对位定位基。

3. 二取代苯的定位效应：

- 苯环上的两个取代基定位导向相同时，亲电试剂将进入共同导向的位置。
- 苯环上的两个取代基定位导向不同时，活化基团的作用大于钝化基团的作用，亲电试剂进入活化基导向的位置。如果原有的两个取代基都是活化基时，强活化基团的影响比弱活化基团的影响大，亲电试剂主要进入强活化基导向的位置。如果原有的两个取代基都是钝化基时，亲电试剂主要进入强钝化基导向的位置。两个基团的定位能力相差不多时，主要得到混合物。

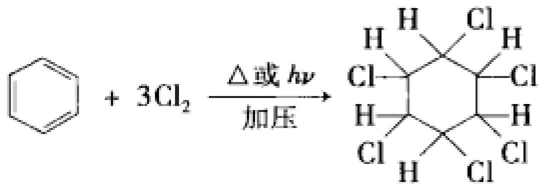
三、芳香亲核取代(nucleophilic aromatic substitution)



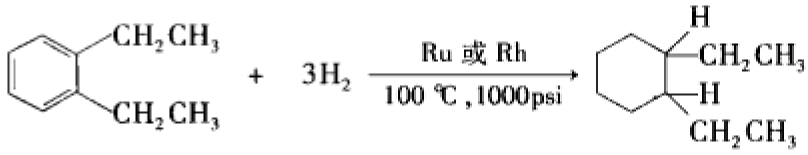
☆ G 为吸电子基团时，亲核加成－消除机理，碳负离子中间体，生产原位取代的产物。G 为给电子基团或 H 时，在强碱(如 $NaNH_2$)作用下生成苯炔中间体，消除－加成机理(也称苯炔机理)，得到原位取代和邻位取代的产物。

四、芳香环的加成反应

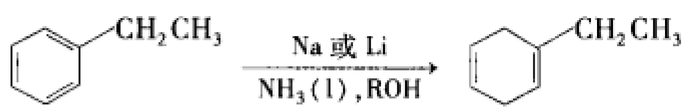
1. 氯化(chlorination)：



2. 催化氢化(catalytic hydrogenation)：

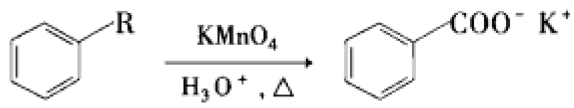


3. Birch 还原：



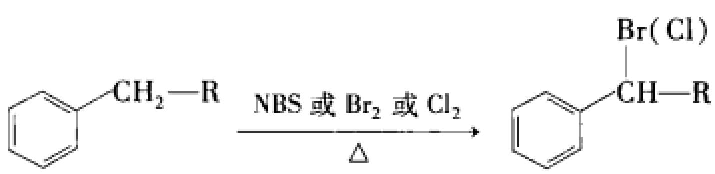
五、芳香环侧链的反应(side-chain reaction aromatic ring)：

1. 高锰酸钾氧化(permanganate oxidation)：



☆ R 基中直接与苯环相连的碳上必须含有氢原子或连不饱和键；不管链多长，均可被氧化为—COOH。

2. 侧链卤代(side-chain halogenation)：



☆ 中间体为苄基型自由基；用于苄基卤的制备，苄基卤是很活泼的卤代烃，可与很多亲核试剂发生亲核取代反应。

Essential Problem-Solving Skills in Chapter 18

1. Predict products and propose mechanisms for the common electrophilic aromatic substitutions: halogenation, nitration, sulfonation, and Friedel-Crafts alkylation and acylation.
2. Draw resonance structures for the sigma complexes resulting from electrophilic attack on substituted aromatic rings. Explain which substituents are activating and which are deactivating, and show why they are ortho, para-directing, or meta-allowing.
3. Predict the position(s) of electrophilic aromatic substitution on molecules containing substituents on one or more aromatic rings.
4. Design syntheses that use the influence of substituents to generate the correct isomers of multisubstituted aromatic compounds.
5. Determine which nucleophilic aromatic substitutions are likely, and propose mechanisms for both the addition-elimination type and the benzyne type.
6. Predict the products of Birch reduction, hydrogenation, and chlorination of aromatic compounds, and use these reactions in syntheses.
7. Explain how the reactions of side chains are affected by the presence of the aromatic ring, predict the

products of side-chain reactions, and use these reactions in syntheses.

8. Predict the products of oxidation and substitution of phenols, and use these reactions in syntheses.

Study Problems

18−19 Define each term and give an example.

(**a**) activating group (**b**) deactivating group (**c**) sigma complex
(**d**) sulfonation (**e**) desulfonation (**f**) nitration
(**g**) ortho, para-director (**h**) meta-director (**i**) resonance stabilization
(**j**) Friedel-Crafts acylation (**k**) Friedel-Crafts alkylation (**l**) Clemmensen reduction
(**m**) Gatterman-Koch synthesis (**n**) benzyne mechanism (**o**) Birch reduction
(**p**) quinone (**q**) benzylic position

18−20 Predict the major products formed when benzene reacts with the following reagents.

(**a**) *t*-butyl bromide, $AlCl_3$ (**b**) 1-chlorobutane, $AlCl_3$
(**c**) isobutyl alcohol + BF_3 (**d**) bromine + a nail
(**e**) isobutylene + HF (**f**) fuming sulfuric acid
(**g**) 1-chloro-2,2-dimethylpropane + $AlCl_3$ (**h**) benzoyl chloride + $AlCl_3$
(**i**) iodine + HNO_3 (**j**) nitric acid + sulfuric acid
(**k**) carbon monoxide, HCl, and $AlCl_3/CuCl$

18−21 Predict the major products formed when isopropylbenzene reacts with the following reagents.

(**a**) 1-equivalent of Br_2 and light (**b**) Br_2 and $FeBr_3$ (**c**) SO_3 and H_2SO_4
(**d**) hot, concd. $KMnO_4$ (**e**) acetyl chloride and $AlCl_3$
(**f**) *n*-propyl chloride and $AlCl_3$

18−22 Show how you would synthesize the following compounds, starting with benzene or toluene and any necessary acyclic reagents. Assume para is the major product (and separable from ortho) in ortho, para mixtures.

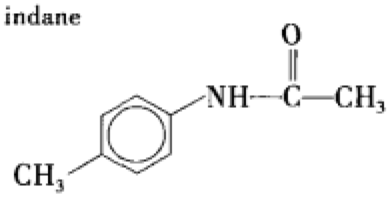
(**a**) 1-phenyl-1-bromobutane (**b**) 1-phenyl-1-methoxybutane
(**c**) 3-phenyl-1-propanol (**d**) ethoxybenzene
(**e**) 1,2-dichloro-4-nitrobenzene (**f**) 1-phenyl-2-propanol
(**g**) *p*-aminobenzoic acid (**h**) 2-methyl-1-phenylbutan-2-ol
(**i**) 5-chloro-2-methylaniline (**j**) 3-nitro-4-bromobenzoic acid
(**k**) 3-nitro-5-bromobenzoic acid (**l**) 4-butylphenol

18−23 Predict the major products of the following reactions.

(**a**) 2,4-dinitrochlorobenzene + $NaOCH_3$
(**b**) phenol + *t*-butyl chloride + $AlCl_3$
(**c**) nitrobenzene + fuming sulfuric acid
(**d**) nitrobenzene + acetyl chloride + $AlCl_3$
(**e**) *p*-methylanisole + acetyl chloride + $AlCl_3$
(**f**) *p*-methylanisole + Br_2, light
(**g**) 1,2-dichloro-4-nitrobenzene + $NaNH_2$
(**h**) *p*-nitrotoluene + Zn + dilute HCl
(**i**) $Ph{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NHPh + CH_3CH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl, AlCl_3$
(**j**) *p*-ethylbenzenesulfonic acid + HNO_3, H_2SO_4
(**k**) *p*-ethylbenzenesulfonic acid + steam

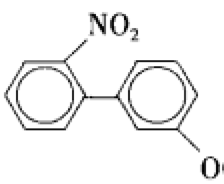
(l) + hot, concd. $KMnO_4$

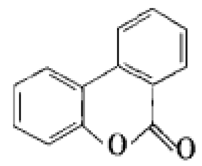
indane

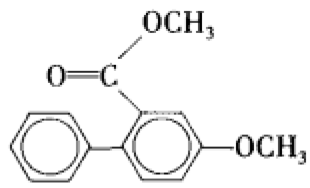
(m)  + acetyl chloride, $AlCl_3$

p-methylacetanilide

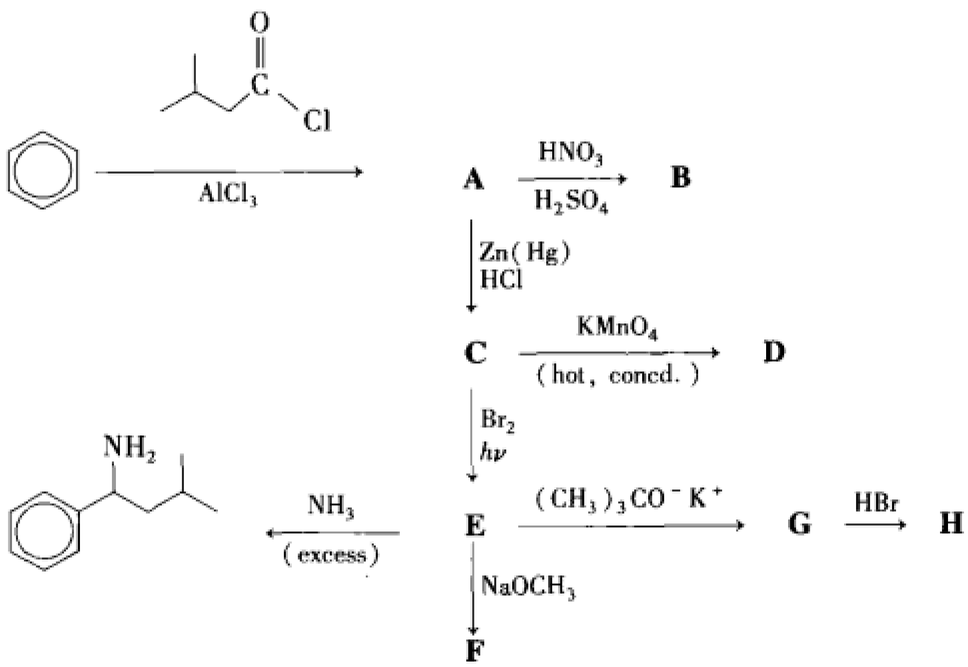
18-24 Predict the major products of bromination of the following compounds, using Br_2 and $FeBr_3$ in the dark.

(a) 

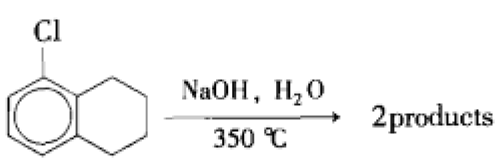
(b) 

(c) 

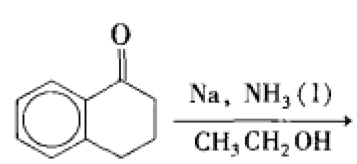
18-25 Give the structures of compounds **A** through **H** in the following series of reactions.



18-26 The following compound reacts with a hot, concentrated solution of NaOH (in a sealed tube) to give a mixture of two products. Propose structures for these products, and give a mechanism to account for their formation.

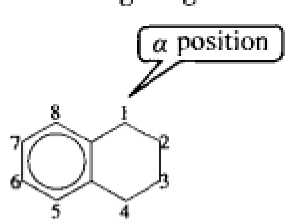


18-27 α-Tetralone undergoes Birch reduction to give an excellent yield of a single product. Predict the structure of the product, and propose a mechanism for its formation.



α-tetralone

18-28 Electrophilic aromatic substitution usually occurs at the 1-position of naphthalene, also called the α position. Predict the major products of the reactions of naphthalene with the following reagents.

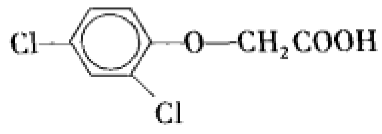


(a) HNO_3, H_2SO_4 **(b)** Br_2, $FeBr_3$ **(c)** CH_3CH_2COCl, $AlCl_3$

(**d**) isobutylene and HF (**e**) cyclohexanol and BF_3 (**f**) fuming sulfuric acid

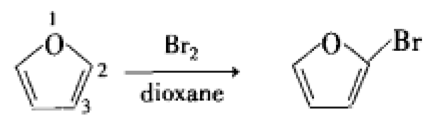
18−29 Triphenylmethanol is insoluble in water, but when it is treated with concentrated sulfuric acid, a bright yellow solution results. As this yellow solution is diluted with water, its color disappears and a precipitate of triphenylmethanol reappears. Suggest a structure for the bright yellow species, and explain this unusual behavior.

18−30 The most common selective herbicide for killing broadleaf weeds is 2,4-dichlorophenoxyacetic acid(2,4-D). Show how you would synthesize 2,4-D from benzene, chloroacetic acid ($ClCH_2COOH$), and any necessary reagents and solvents.



2,4-dichlorophenoxyacetic acid(2,4-D)

18−31 Furan undergoes electrophilic aromatic substitution more readily than benzene; mild reagents and conditions are sufficient. For example, furan reacts with bromine to give 2-bromofuran.

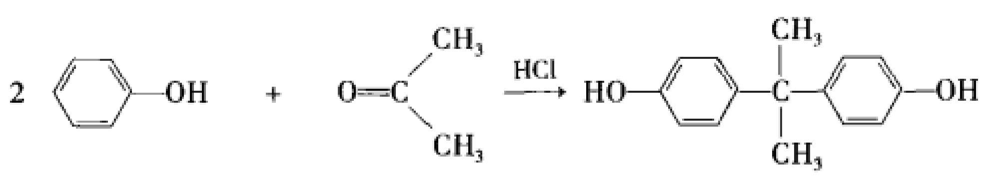


furan 2-bromofuran

(**a**) Propose mechanisms for the bromination of furan at the 2-position and at the 3-position. Draw the resonance structures of each sigma complex, and compare their stabilities.

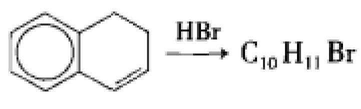
(**b**) Explain why furan undergoes bromination (and other electrophilic aromatic substitutions) primarily at the 2-position.

*__18−32__ *Bisphenol A* is an important component of many polymers, including polycarbonates, polyurethanes, and epoxy resins. It is synthesized form phenol and acetone with HCl as a catalyst. Propose a mechanism for this reaction.



phenol acetone bisphenol A

18−33 The compound shown reacts with HBr to give a product of molecular formula $C_{10}H_{11}Br$.



(**a**) Propose a mechanism for this reaction, and predict the structure of the product. Carefully show the resonance stabilization of the intermediate.

(**b**) When this reaction takes place in the presence of a free-radical initiator, the product is a different isomer of formula $C_{10}H_{11}Br$. Propose a structure for this second product, and give a mechanism to account for its formation.

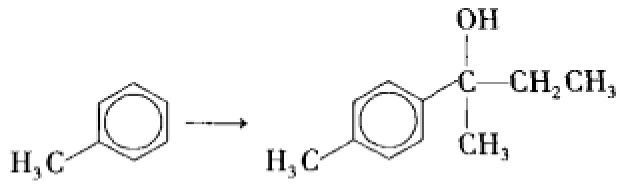
18−34 Unlike most other electrophilic aromatic substitutions, sulfonation is often reversible (see Section 18−4). When one sample of toluene is sulfonated at 0 ℃ and another sample is sulfonated at 100 ℃, the following ratios of substitution products result:

Isomer of the Product	*Reaction Temperature*	
	0 ℃	100 ℃
o-toluenesulfonic acid	43%	13%
m-toluenesulfonic acid	4%	8%
p-toluenesulfonic acid	53%	79%

(**a**) Explain the change in the product ratios when the temperature is increased.

(**b**) Predict what will happen when the product mixture from the reaction at 0 ℃ is heated to 100 ℃.

18−35 Devise a synthesis of the following compound, starting from toluene and using any necessary reagents.



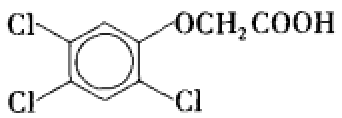
* **18－36** When anthracene is added to the reaction of chlorobenzene with concentrated NaOH at 350 ℃, an interesting Diels-Alder adduct of formula $C_{20}H_{14}$ results. The proton NMR spectrum of the product shows a singlet of area 2 around $\delta 3$ and a broad singlet of area 12 around $\delta 7$. Propose a structure for the product, and explain why one of the aromatic rings of anthracene reacted as a diene.

18－37 In Chapter 16, we saw that Agent Orange contains (2,4,5-trichlorophenoxy) acetic acid, called 2,4,5-T. This compound is synthesized by the partial reaction of 1,2,4,5-tetrachlorobenzene with sodium hydroxide, followed by reaction with sodium chloroacetate, $ClCH_2CO_2Na$.

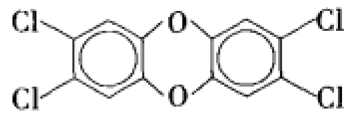
(a) Draw the structures of these compounds, and write equations for these reactions.

(b) One of the impurities in the Agent Orange used in Vietnam was 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD), often incorrectly called "dioxin." Propose a mechanism to show how 2,3,7,8-TCDD is formed in the synthesis of 2,4,5-T.

(c) Show how the TCDD contamination might be eliminated, both after the first step and on completion of the synthesis.

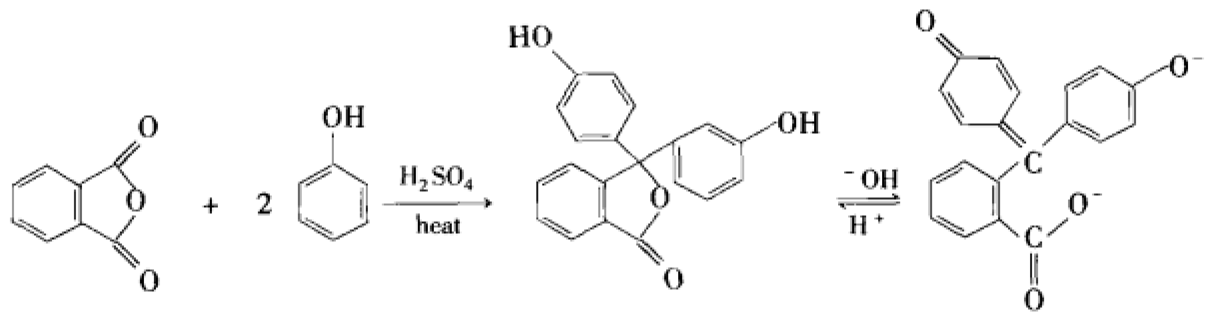


2,4,5-T



2,3,7,8-tetrachlorodibenzodioxin(TCDD)

* **18－38** Phenolphthalein, a common nonprescription laxative, is also an acid-base indicator that is colorless in acid and red in base. Phenolphthalein is synthesized by the acid-catalyzed reaction of phthalic anhydride with 2 equivalents of phenol.



phthalic anhydride　　phenolphthalein　　red dianion

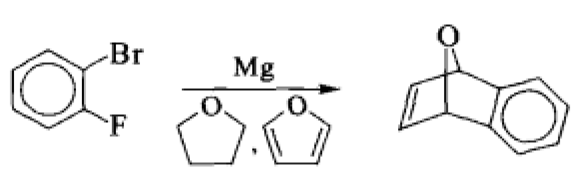
(a) Propose a mechanism for the synthesis of phenolphthalein.

(b) Propose a mechanism for the conversion of phenolphthalein to its red dianion in base.

(c) Use resonance structures to show that the two phenolic oxygen atoms are equivalent (each with half a negative charge) in the red phenolphthalein dianion.

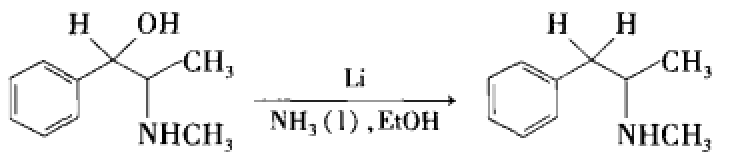
* **18－39** Because the SO_3H group can be added to a benzene ring and removed later, it is sometimes called a blocking group. Show how, 2,6-dibromotoluene can be made from toluene using sulfonation and desulfonation as intermediate steps in the synthesis.

* **18－40** A graduate student tried to make *o*-fluorophenylmagnesium bromide by adding magnesium to an ether solution of *o*-fluorobromobenzene. After obtaining puzzling results with this reaction, she repeated the reaction by using as solvent some tetrahydrofuran that contained a small amount of furan. From this reaction, she isolated a fair yield of the compound that follows. Propose a mechanism for its formation.



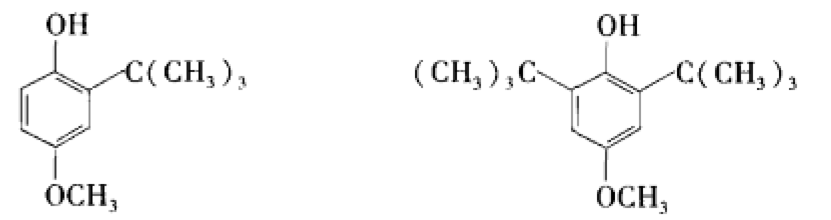
* **18－41** A common illicit synthesis of methamphetamine involves an interesting variation of the Birch reduction. A solution of

ephedrine in alcohol is added to liquid ammonia, followed by several pieces of lithium metal. The Birch reduction usually reduces the aromatic ring (Section 18−13C), but in this case it eliminates the hydroxyl group of ephedrine to give methamphetamine. *Propose a mechanism, similar to that for the Birch reduction*, to explain this unusual course of the reaction.



ephedrine methamphetamine

18−42 The antioxidants BHA and BHT are commonly used as food preservatives. Show how BHA and BHT can be made from phenol and hydroquinone.



BHA BHT

18−43 When 1,2-dibromo-3,5-dinitrobenzene is treated with excess NaOH at 50 ℃, only one of the bromine atoms is replaced. Draw an equation for this reaction, showing the product you expect. Give a mechanism to account for the formation of your proposed product.

Chapter 19
Ketones and Aldehydes

19-1 Carbonyl Compounds

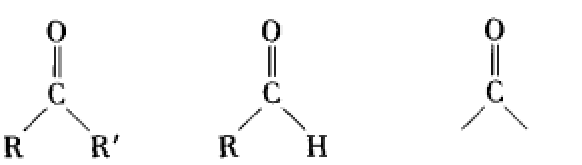
We will study compounds containing the **carbonyl group** (C═O) in detail because they are of central importance to organic chemistry, biochemistry, and biology. Some of the common types of carbonyl compounds are listed in Table 19-1.

TABLE 19-1 Some Common Classes of Carbonyl Compounds

Class	General Formula	Class	General Formula
ketones (酮)	R—C(═O)—R′	aldehydes (醛)	R—C(═O)—H
carboxylic acids (羧酸)	R—C(═O)—OH	acid chlorides (酰氯)	R—C(═O)—Cl
esters(酯)	R—C(═O)—O—R′	amides(酰胺)	R—C(═O)—NH_2

Carbonyl compounds are everywhere. In addition to their uses as reagents and solvents, they are constituents of fabrics, flavorings, plastics, and drugs. Naturally occurring carbonyl compounds include proteins, carbohydrates, and nucleic acids that make up all plants and animals. In the next few chapters, we will discuss the properties and reactions of simple carbonyl compounds. Then, in Chapters 24 and 25, we apply this carbonyl chemistry to carbohydrates, nucleic acids, and proteins.

The simplest carbonyl compounds are ketones and aldehydes. A **ketone** has two alkyl (or aryl) groups bonded to the carbonyl carbon atom. An **aldehyde** has one alkyl (or aryl) group and one hydrogen atom bonded to the carbonyl carbon atom.



ketone　　aldehyde　　carbonyl group

condensed structures:　RCOR′　　RCHO

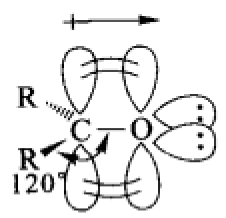
Ketone: Two alkyl groups bonded to a carbonyl group.

Aldehyde: One alkyl group and one hydrogen bonded to a carbonyl group.

Ketones and aldehydes are similar in structure, and they have similar properties. There are some differences, however, particularly in their reactions with oxidizing agents and with nucleophiles. In most cases, aldehydes are more reactive than ketones, for reasons we discuss shortly.

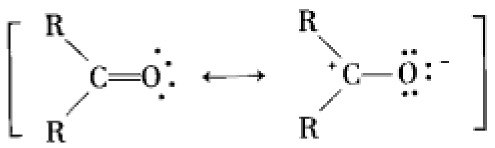
19-2 Structure of the Carbonyl Group

The carbonyl carbon atom is sp^2 hybridized and bonded to three other atoms through coplanar sigma bonds oriented about 120° apart. The unhybridized p orbital overlaps with a p orbital of oxygen to form a pi bond. The double bond between carbon and oxygen is similar to an alkene C=C double bond, except that the carbonyl double bond is shorter, stronger, and polarized.



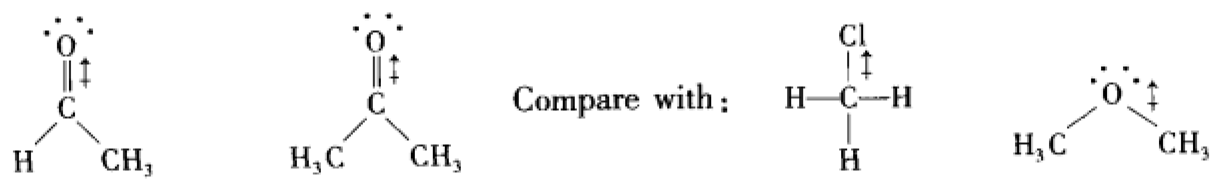
	length	*energy*
ketone C=O bond	1.23 Å	745 kJ/mol
alkene C=C bond	1.34 Å	611 kJ/mol

The double bond of the carbonyl group has a large dipole moment because oxygen is more electronegative than carbon, and the bonding electrons are not shared equally. In particular, the less tightly held pi electrons are pulled more strongly toward the oxygen atom, giving ketones and aldehydes larger dipole moments than most alkyl halides and ethers. We can use resonance forms to symbolize this unequal sharing of the pi electrons.



major minor

The first resonance form is more important because it involves more bonds and less charge separation. The contribution of the second structure is evidenced by the large dipole moments of the ketones and aldehydes shown here.



μ = 2.7 D acetaldehyde (乙醛) μ = 2.9 D acetone (丙酮) μ = 1.9 D chloromethane μ = 1.30 D dimethyl ether

This polarization of the carbonyl group contributes to the reactivity of ketones and aldehydes: The positively polarized carbon atom acts as an electrophile (Lewis acid), and the negatively polarized oxygen acts as a nucleophile (Lewis base).

19-3 Physical Properties of Ketones and Aldehydes

Polarization of the carbonyl group creates dipole-dipole attractions between the molecules of ketones and aldehydes, resulting in higher boiling points than for hydrocarbons and ethers of similar molecular weights. Ketones and aldehydes have no O—H or N—H bonds, however, so their molecules cannot form hydrogen bonds with each other. Their boiling points are therefore lower than those of alcohols of similar molecular weight. The follow-

ing compounds of molecular weight 58 or 60 are ranked in order of increasing boiling points. The ketone and the aldehyde are more polar and higher-boiling than the ether and the alkane, but lower-boiling than the hydrogen-bonded alcohol.

$CH_3CH_2CH_2CH_3$	$CH_3—O—CH_2CH_3$	$CH_3CH_2—C(=O)—H$	$CH_3—C(=O)—CH_3$	$CH_3CH_2CH_2—OH$
butane	methoxyethane	propanal	acetone	1-propanol
bp 0 ℃	bp 8 ℃	bp 49 ℃	bp 56 ℃	bp 97 ℃

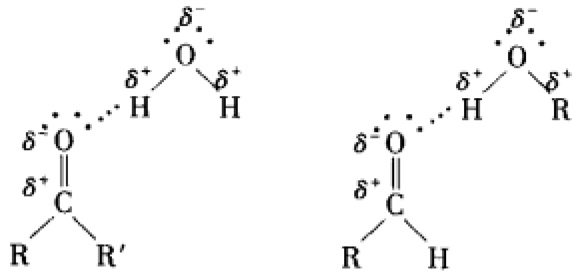
The melting points boiling points, and water solubilities of some representative ketones and aldehydes are given in Table 19-2.

TABLE 19-2 Physical Properties of Some Representative Ketones and Aldehydes

Structure	mp/℃	bp/℃	Density/($g\cdot cm^{-3}$)	H_2O Solubility/%
Ketones				
CH_3COCH_3	-95	56	0.79	∞
$CH_3COCH_2CH_3$	-86	80	0.81	25.6
$CH_3COCH_2CH_2CH_3$	-78	102	0.81	5.5
$CH_3CH_2COCH_2CH_3$	-41	101	0.81	4.8
$CH_3CO(CH_2)_3CH_3$	-57	127	0.83	1.6
$CH_3CH_2COCH_2CH_2CH_3$		124	0.82	
$CH_3CO(CH_2)_4CH_3$	-36	151	0.81	1.4
$CH_3CH_2CO(CH_2)_3CH_3$	-39	147	0.82	0.4
$(CH_3CH_2CH_2)_2CO$	-34	144	0.82	
$(CH_3)_2C{=}CHCOCH_3$	-59	131	0.86	
$CH_2{=}CHCOCH_3$	-6	80	0.86	
	-16	157	0.94	15
$C_6H_5COCH_3$	21	202	1.02	0.5
$C_6H_5COCH_2CH_3$	21	218		
$C_6H_5COC_6H_5$	48	305	1.08	
Aldehydes				
HCHO or CH_2O	-92	-21	0.82	55
CH_3CHO	-123	21	0.78	∞
CH_3CH_2CHO	-81	49	0.81	20
$CH_3(CH_2)_2CHO$	-97	75	0.82	7.1
$(CH_3)_2CHCHO$	-66	61	0.79	11
$CH_3(CH_2)_3CHO$	-91	103	0.82	
$(CH_3)_2CHCH_2CHO$	-51	93	0.80	
$CH_3(CH_2)_4CHO$	-56	129	0.83	0.1
$CH_3(CH_2)_5CHO$	-45	155	0.85	0.02
$CH_2{=}CH—CHO$	-88	53	0.84	30
$CH_3—CH{=}CH—CHO$	-77	104	0.86	18
C_6H_5CHO	-56	179	1.05	0.3

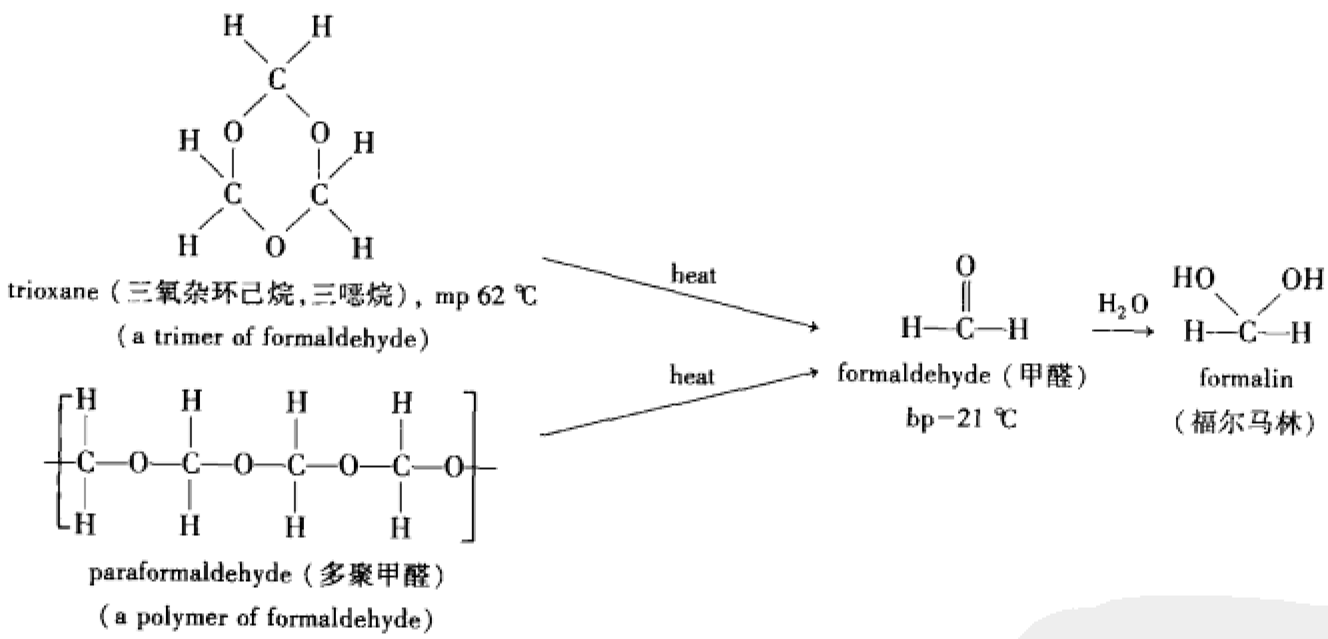
Although pure ketones and aldehydes cannot engage in hydrogen bonding with each other, they have lone pairs of electrons and can act as hydrogen bond acceptors with other compounds having O—H or N—H bonds. For example, the —OH hydrogen of water or an alcohol can form a hydrogen bond with the unshared electrons on

a carbonyl oxygen atom.

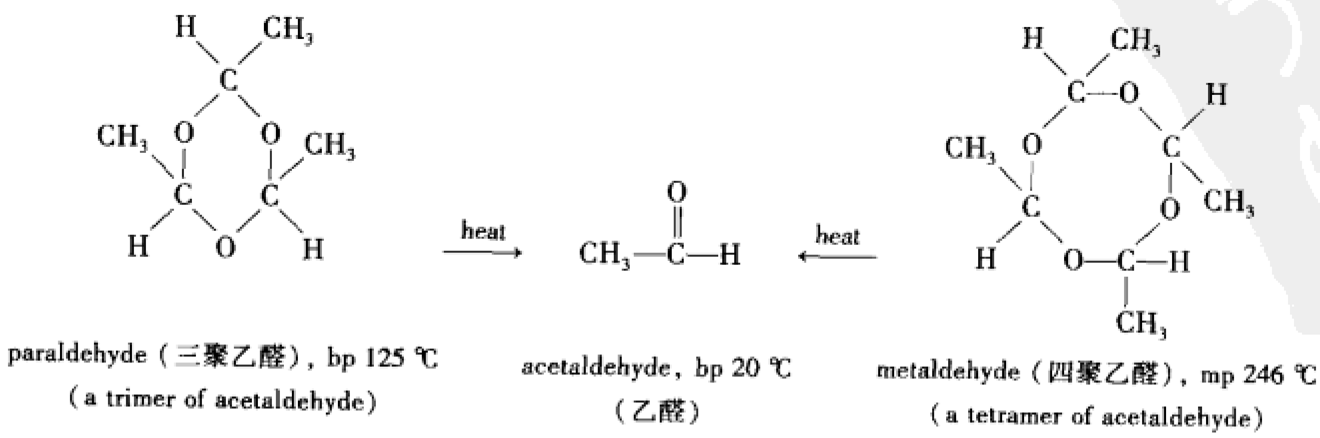


Because of this hydrogen bonding, ketones and aldehydes are good solvents for polar hydroxylic substances such as alcohols. They are also remarkably soluble in water. Table 19-2 shows that acetaldehyde and acetone are miscible (soluble in all proportions) with water. Other ketones and aldehydes with up to four carbon atoms are fairly soluble in water. These solubility properties are similar to those of ethers and alcohols, which also engage in hydrogen bonding with water.

Formaldehyde and acetaldehyde are the most common aldehydes. Formaldehyde is a gas at room temperature, so it is often stored and used as a 40% aqueous solution called *formalin*. When dry formaldehyde is needed, it can be generated by heating one of its solid derivatives, usually *trioxane* or *paraformaldehyde*. Trioxane is a cyclic *trimer*, containing three formaldehyde units. Paraformaldehyde is a linear *polymer*, containing many formaldehyde units. These solid derivatives form spontaneously when a small amount of acid catalyst is added to pure formaldehyde.



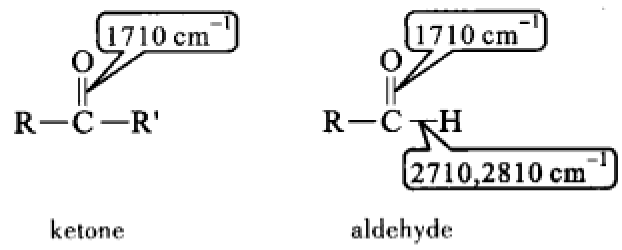
Acetaldehyde boils near room temperature, and it can be handled as a liquid. Acetaldehyde is also used as a trimer (*paraldehyde*) and a tetramer (*metaldehyde*), formed from acetaldehyde under acid catalysis. Heating either of these compounds provides dry acetaldehyde. Paraldehyde is used in medicines as a sedative, and metaldehyde is used as a bait and poison for snails and slugs.



19-4 Spectroscopy of Ketones and Aldehydes

19-4A Infrared Spectra of Ketones and Aldehydes

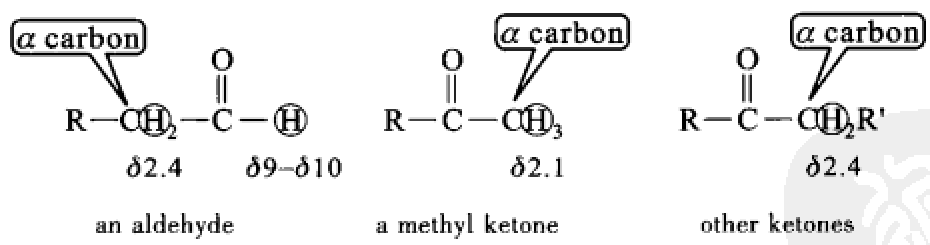
The carbonyl (C=O) stretching vibrations of simple ketones and aldehydes occur around 1 710 cm^{-1}. Because the carbonyl group has a large dipole moment, these absorptions are very strong. In addition to the carbonyl absorption, an aldehyde shows a set of two low-frequency C—H stretching absorptions around 2 710 and 2 810 cm^{-1}.



Conjugation lowers the carbonyl stretching frequencies of ketones and aldehydes because the partial pi bonding character of the single bond between the conjugated double bonds reduces the electron density of the carbonyl pi bond. The stretching frequency of this weakened carbonyl bond is lowered to about 1 685 cm^{-1}. Ring strain has the opposite effect, raising the carbonyl stretching frequency in ketones with three-, four-, and five-membered rings.

19-4B Proton NMR Spectra of Ketones and Aldehydes

When considering the proton NMR spectra of ketones and aldehydes, we are interested primarily in the protons bonded to the carbonyl group (aldehyde protons) and the protons bonded to the adjacent carbon atom (the α carbon atom). Aldehyde protons normally absorb at chemical shifts between $\delta 9$ and $\delta 10$. The aldehyde proton's absorption may be split ($J = 1$ to 5 Hz) if there are protons on the α carbon atom. Protons on the α carbon atom of a ketone or aldehyde usually absorb at a chemical shift between $\delta 2.1$ and $\delta 2.4$ if there are no other electron-withdrawing groups nearby. Methyl ketones are characterized by a singlet at about $\delta 2.1$.



19-4C Carbon NMR Spectra of Ketones and Aldehydes

Carbonyl carbon atoms have chemical shifts around 200 in the carbon NMR spectrum. Because they have no hydrogens attached, ketone carbonyl carbon atoms usually give weak absorptions. The α carbon atoms usually absorb at chemical shifts of about 30 to 40.

19-5 Industrial Importance of Ketones and Aldehydes

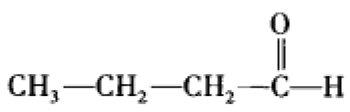
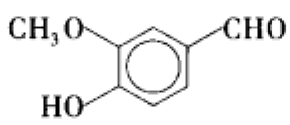
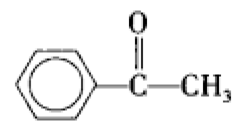
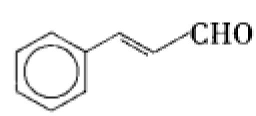
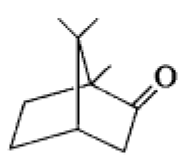
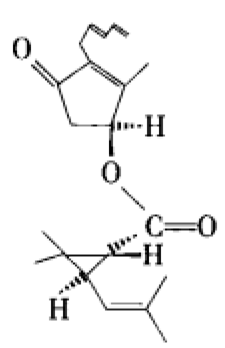
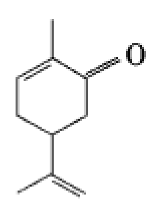
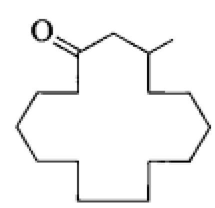
In the chemical industry, ketones and aldehydes are used as solvents, starting materials, and reagents for the synthesis of other products. Although formaldehyde is well known as the formalin solution used to preserve biological specimens, most of the 4 billion kilograms of formaldehyde produced each year is used to make Bakelite®,

phenol-formaldehyde resins, urea-formaldehyde glues, and other polymeric products. Acetaldehyde is used primarily as a starting material in the manufacture of acetic acid, polymers, and drugs.

Acetone is the most important commercial ketone, with over 3 billion kilograms used each year. Both acetone and methyl ethyl ketone (2-butanone) are common industrial solvents. These ketones dissolve a wide range of organic materials, have convenient boiling points for easy distillation, and have low toxicities.

Many other ketones and aldehydes are used as flavorings and additives to foods, drugs, and other products. For example, benzaldehyde is the primary component of almond extract, and (−)-carvone gives spearmint chewing gum its minty flavor. Table 19−3 lists some simple ketones and aldehydes with well-known odors and flavors. *Pyrethrin*, isolated from pyrethrum flowers, is commercially extracted for use as a "natural" insecticide. "Natural" or not, pyrethrin can cause severe allergic reactions, nausea, vomiting, and other toxic effects in animals.

TABLE 19−3 Ketones and Aldehydes Used in Household Products

				
	butyraldehyde (丁醛)	vanillin(香兰素)	acetophenone (苯乙酮)	*trans*-cinnamaldehyde (顺-肉桂醛)
Odor:	buttery (奶油)	vanilla (香草)	pistachio (阿月浑子)	cinnamon (肉桂)
Uses:	margarine, foods	foods, perfumes	ice cream	candy, foods, drugs
				
	camphor (莰酮)	pyrethrin (除虫菊酯)	carvone (香芹酮)	muscone (麝香酮)
Odor:	"camphoraceous" (樟脑特有的)	floral	(−) enantiomer: spearmint (+) enantiomer: caraway seed (口蒿种子)	musky aroma (麝香)
Uses:	liniments, inhalants	plant insecticide	candy, toothpaste, etc.	perfumes

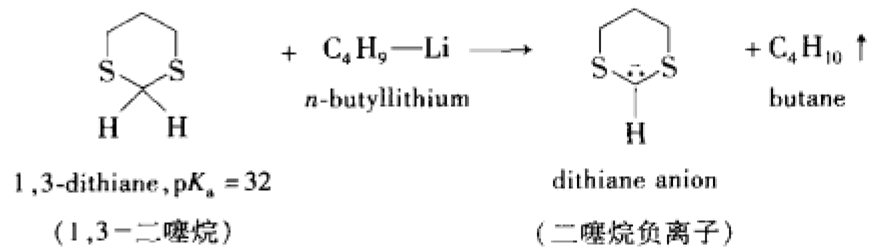
19−6 Syntheses of Ketones and Aldehydes

In studying reactions of other functional groups, we have already encountered some of the best methods for making ketones and aldehydes. In the following sections, we consider additional syntheses of ketones and aldehydes that we have not covered before. These syntheses form ketones and aldehydes from carboxylic acids, nitriles, acid chlorides, and alkyl halides (used to alkylate 1,3-dithiane).

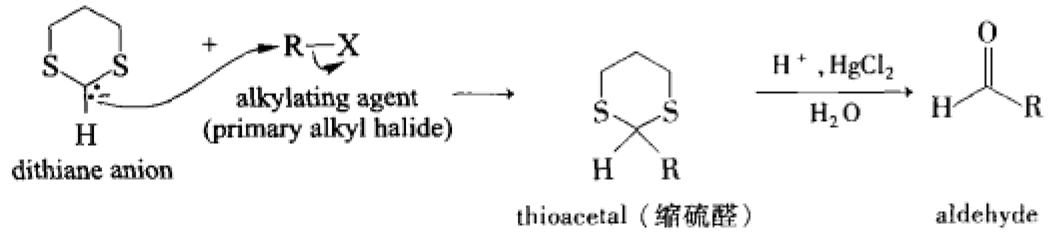
19−6A Synthesis of Ketones and Aldehydes Using 1,3-Dithianes

1,3-Dithiane is a weak proton acid ($pK_a = 32$) that can be deprotonated by strong bases such as *n*-butyllithium.

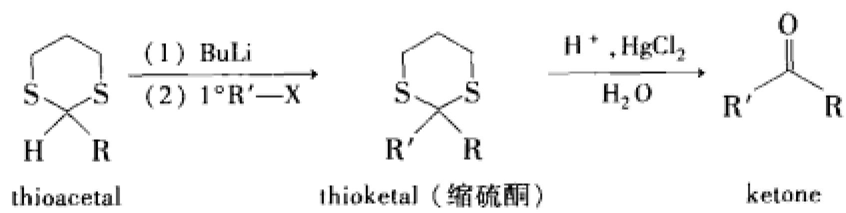
The resulting carbanion is stabilized by the electronwithdrawing effect of two highly polari-zable sulfur atoms.



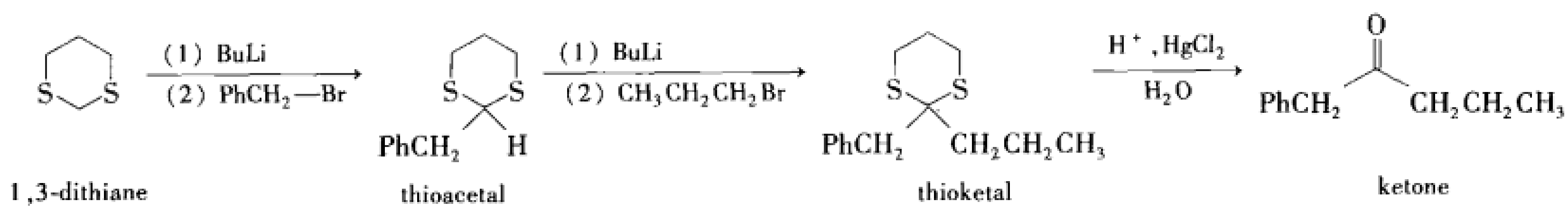
Alkylation of the dithiane anion by a primary alkyl halide or tosylate gives a thioacetal (sulfur acetal) that can be hydrolyzed using an acidic solution of mercuric chloride. The product is an aldehyde bearing the alkyl group that was added by the alkylating agent. This is a useful synthesis of aldehydes bearing primary alkyl groups.



Alternatively, the thioacetal can be alkylated once more to give a thioketal. Hydrolysis of the thioketal gives a ketone.



For example, 1-phenyl-2-pentanone may be synthesized as shown:



In each of these sequences, dithiane is alkylated once or twice, then hydrolyzed to give a carbonyl group bearing the alkyl group(s) used in the alkylation. We often consider dithiane to be a synthetic equivalent of a carbonyl group that can be made nucleophilic and alkylated.

PROBLEM 19-1

Show how you would use the dithiane method to make the following ketones and aldehydes.

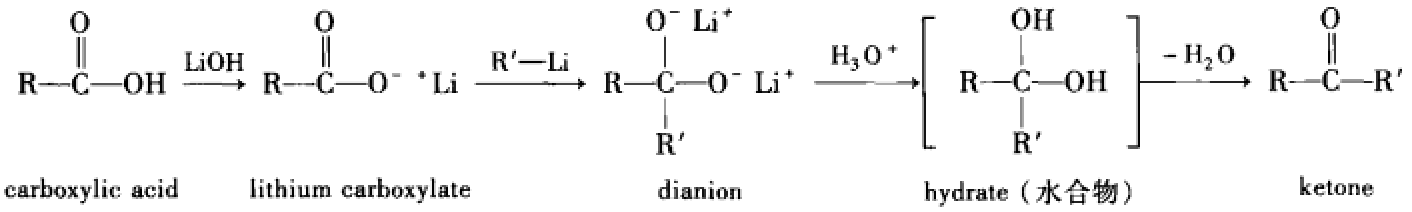
(**a**) 3-phenylpropanal (**b**) 4-phenyl-2-hexanone

(**c**) dibenzyl ketone (**d**) 1-cyclohexyl-4-phenyl-2-butanone

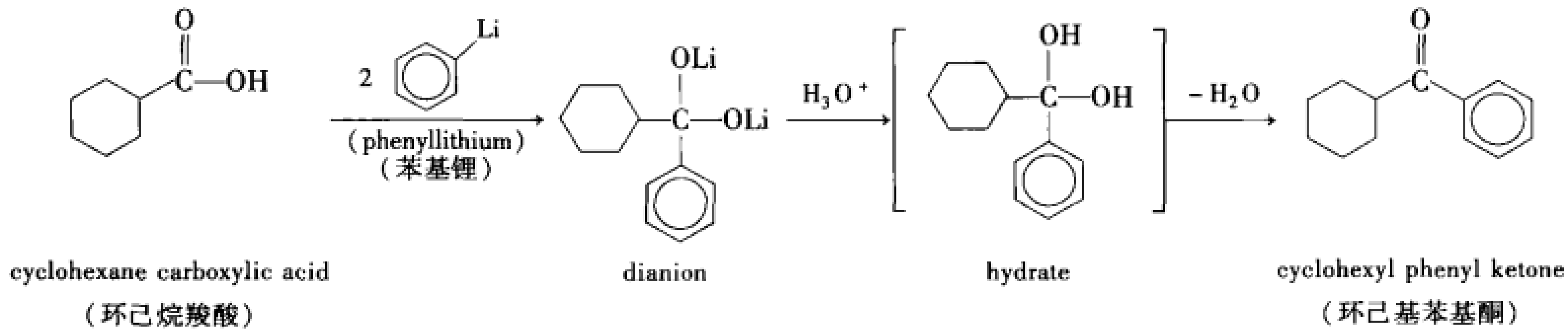
19-6B Synthesis of Ketones from Carboxylic Acids

Organolithium reagents can be used to synthesize ketones from carboxylic acids. Organolithiums are so reactive

toward carbonyls that they attack the lithium salts of carboxylate anions to give dianions. Protonation of the dianion forms the hydrate of a ketone, which quickly loses water to give the ketone.

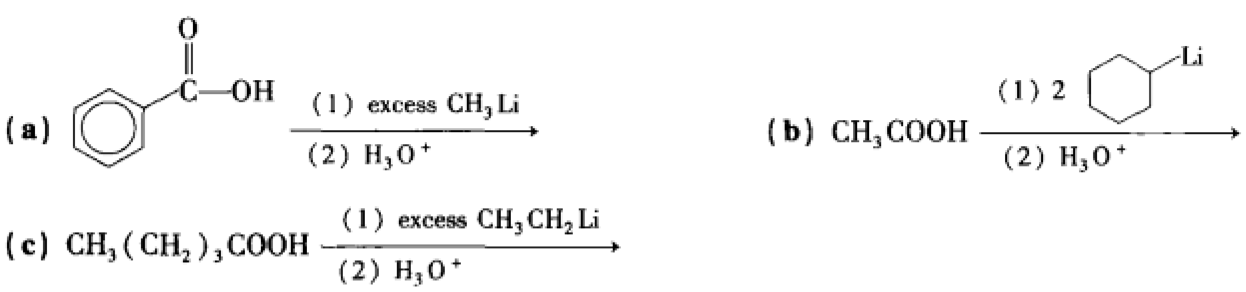


If the organolithium reagent is inexpensive, we can simply add two equivalents to the carboxylic acid. The first equivalent generates the carboxylate salt, and the second attacks the carbonyl group. Subsequent protonation gives the ketone.



PROBLEM 19-2

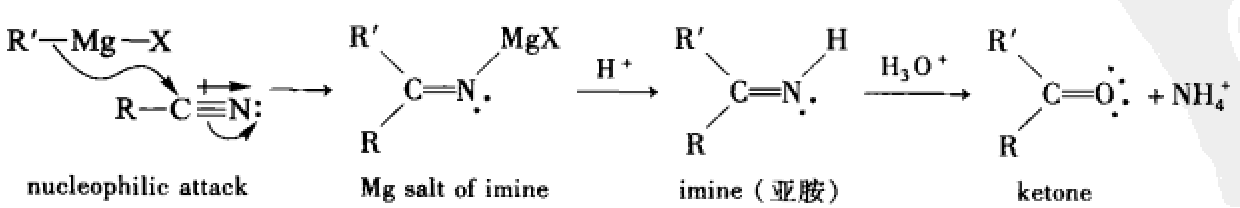
Predict the products of the following reactions.



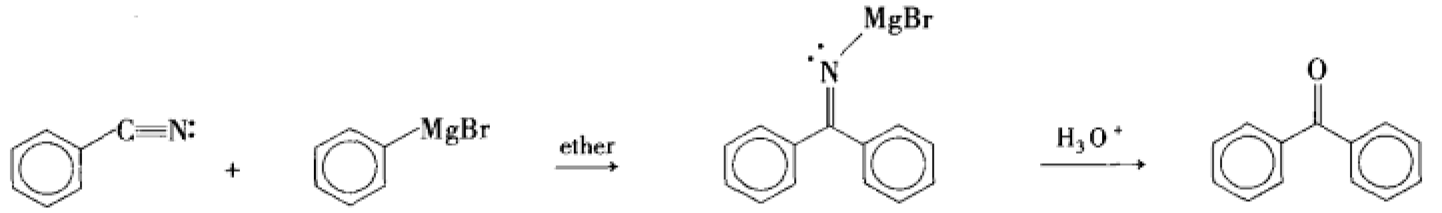
19-6C Synthesis of Ketones from Nitriles

Nitriles can also be used as starting materials for the synthesis of ketones. Discussed in Chapter 22, nitriles are compounds containing the cyano (—C≡N) functional group. Since nitrogen is more electronegative than carbon, the —C≡N triple bond is polarized like the C=O bond of the carbonyl group. Nucleophiles can add to the —C≡N triple bond by attacking the electrophilic carbon atom.

A Grignard or organolithium reagent attacks a nitrile to give the magnesium salt of an imine. Acidic hydrolysis of the imine leads to the ketone. Note that the ketone is formed during the hydrolysis after any excess Grignard reagent has been destroyed; thus, the ketone is not attacked.



Example



benzonitrile (苄腈) + phenylmagnesium bromide (苯基溴化镁) → benzophenone imine (二苯酮亚胺) (magnesium salt) → benzophenone (80%) [苯酮(俗), 二苯酮]

PROBLEM 19-3

Predict the products of the following reactions.

(a) $CH_3CH_2CH_2CH_2—C≡N + CH_3CH_2—MgBr$, then H_3O^+

(b) benzyl bromide + sodium cyanide

(c) product of (b) + cyclopentylmagnesium bromide, then acidic hydrolysis

PROBLEM 19-4

Show how the following transformations may be accomplished in good yield. You may use any additional reagents that are needed.

(a) bromobenzene → propiophenone

(b) CH_3CH_2CN → 3-heptanone

(c) pentanoic acid → 3-heptanone

(d) toluene → benzyl cyclopentyl ketone

19-6D Synthesis of Aldehydes and Ketones from Acid Chlorides

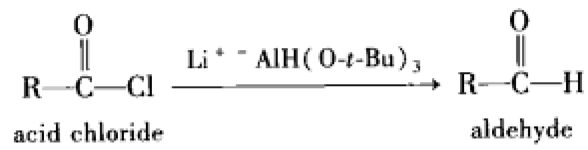
Because aldehydes are easily oxidized to acids, one might wonder whether acids are easily reduced back to aldehydes. Aldehydes tend to be more reactive than acids, however, and reducing agents that are strong enough to reduce acids also reduce aldehydes even faster.

$$\underset{\text{acid}}{R—\overset{\overset{O}{\|}}{C}—OH} \xrightarrow[\text{(slow)}]{LiAlH_4} \left[\underset{\substack{\text{aldehyde}\\ \text{(not isolable)}}}{R—\overset{\overset{O}{\|}}{C}—H}\right] \xrightarrow[\text{(fast)}]{LiAlH_4} \underset{\text{alkoxide (醇盐)}}{R—CH_2—O^-}$$

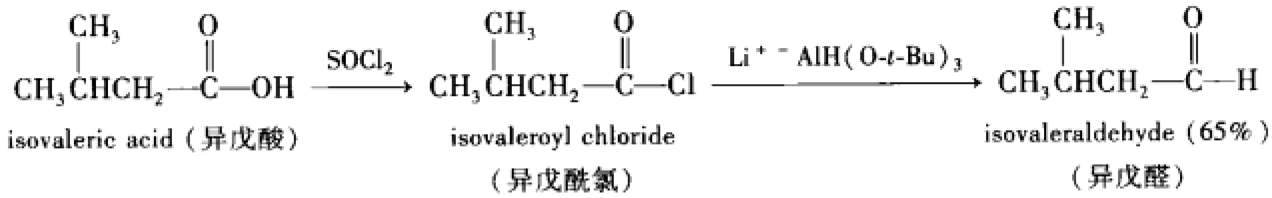
Acids can be reduced to aldehydes by first converting them to a functional group that is easier to reduce than an aldehyde: the acid chloride. Acid chlorides (acyl chlorides) are reactive derivatives of carboxylic acids in which the acidic hydroxyl group is replaced by a chlorine atom. Acid chlorides are often synthesized by treatment of carboxylic acids with thionyl chloride, $SOCl_2$.

$$\underset{\text{acid}}{R—\overset{\overset{O}{\|}}{C}—OH} + \underset{\text{thionyl chloride (亚硫酰氯)}}{Cl—\overset{\overset{O}{\|}}{S}—Cl} \longrightarrow \underset{\text{acid chloride}}{R—\overset{\overset{O}{\|}}{C}—Cl} + HCl + SO_2\uparrow$$

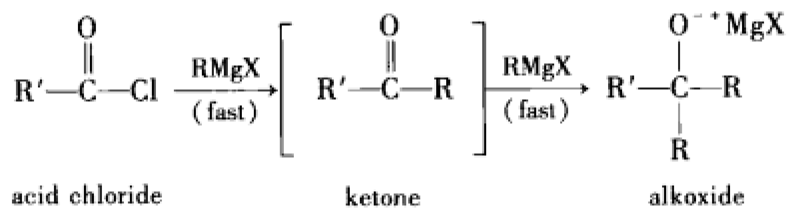
Strong reducing agents like $LiAlH_4$ reduce acid chlorides all the way to primary alcohols. Lithium aluminum tri (*t*-butoxy) hydride, $LiAlH(O\text{-}t\text{-}Bu)_3$, is a milder reducing agent that reacts faster with acid chlorides than with aldehydes. Reduction of acid chlorides with lithium aluminum tri (*t*-butoxy) hydride gives good yields of aldehydes.



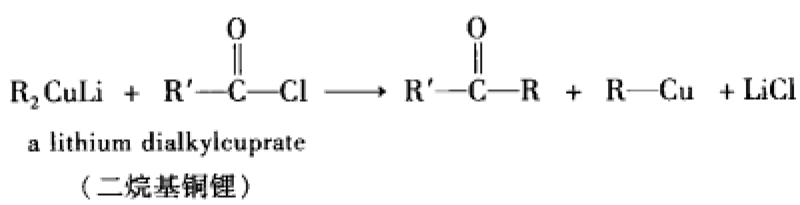
Example



Synthesis of Ketones Grignard and organolithium reagents react with acid chlorides much like hydride reagents: They add R^- where a hydride reagent would add H^-. Grignard and organolithium reagents add to acid chlorides to give ketones, but they add again to the ketones to give tertiary alcohols.



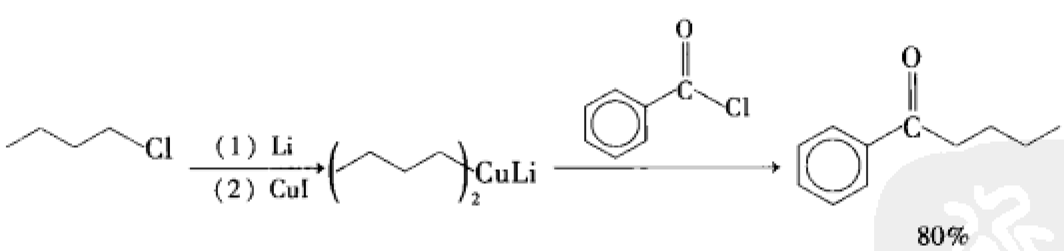
To stop at the ketone stage, a weaker organometallic reagent is needed: one that reacts faster with acid chlorides than with ketones. A **lithium dialkylcuprate (Gilman reagent)** is such a reagent.



The lithium dialkylcuprate is formed by the reaction of two equivalents of the corresponding organolithium reagent with cuprous iodide.

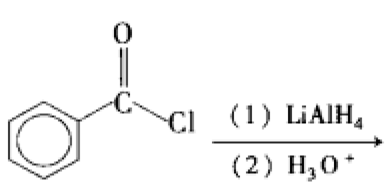
$$2\ \ R\text{—}Li + CuI \longrightarrow R_2CuLi + LiI$$

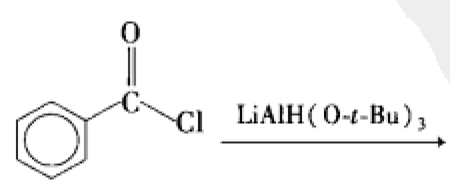
Example

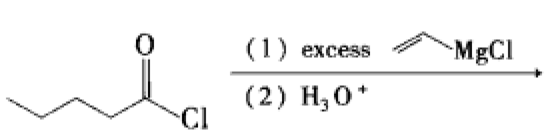


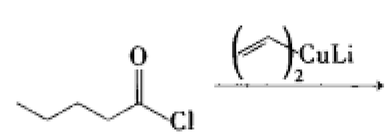
PROBLEM 19−5

Predict the products of the following reactions:

(a) 

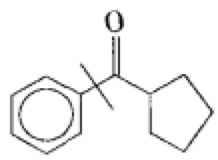
(b) 

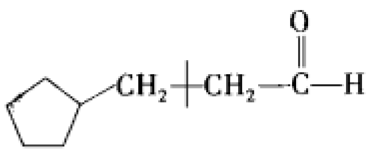
(c) 

(d) 

SOLVED PROBLEM 19-1

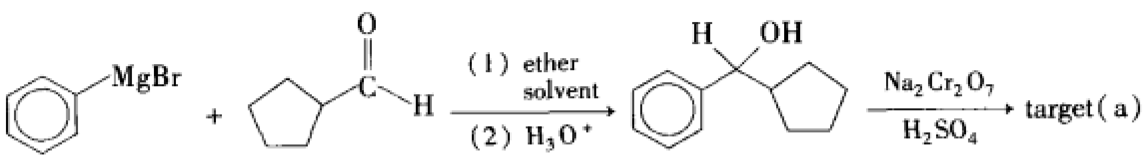
Show how you would synthesize each compound from starting materials containing no more than six carbon atoms.

(a) 

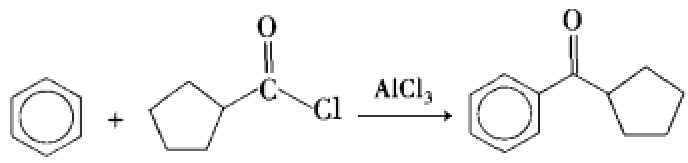
(b) 

SOLUTION

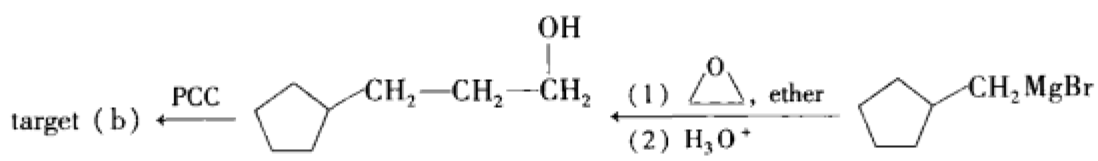
(a) This compound is a ketone with 12 carbon atoms. The carbon skeleton might be assembled from two six-carbon fragments using a Grignard reaction, which gives an alcohol that is easily oxidized to the target compound.



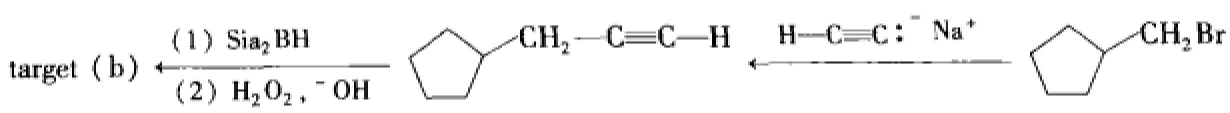
An alternative route to the target compound involves Friedel-Crafts acylation.



(b) This compound is an aldehyde with eight carbon atoms. An aldehyde might come from oxidation of an alcohol (possibly a Grignard product) or hydroboration of an alkyne. If we use a Grignard, the restriction to six-carbon starting materials means we need to add two carbons to a methylcyclopentyl fragment, ending in a primary alcohol. Grignard addition to an epoxide does this.

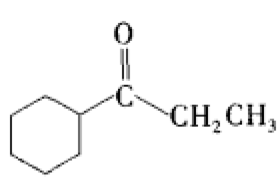


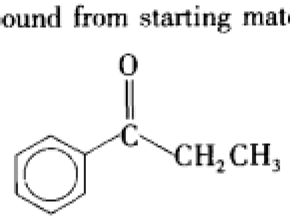
Alternatively, we could construct the carbon skeleton using acetylene as the two-carbon fragment. The resulting terminal alkyne undergoes hydroboration to the correct aldehyde.

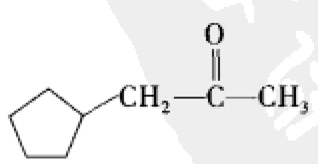


PROBLEM 19-6

Show how you would synthesize each compound from starting materials containing no more than six carbon atoms.

(a) 

(b) 

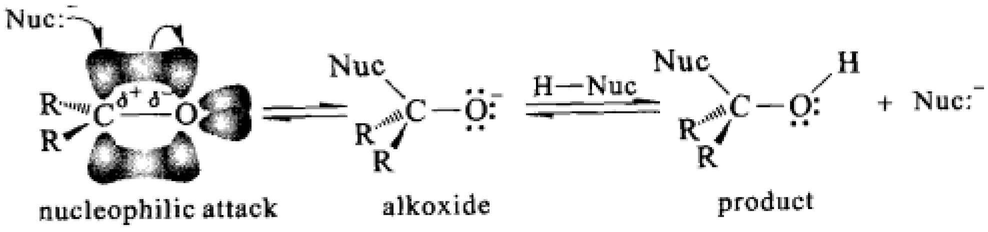
(c) 

19-7 Reactions of Ketones and Aldehydes: Nucleophilic Addition

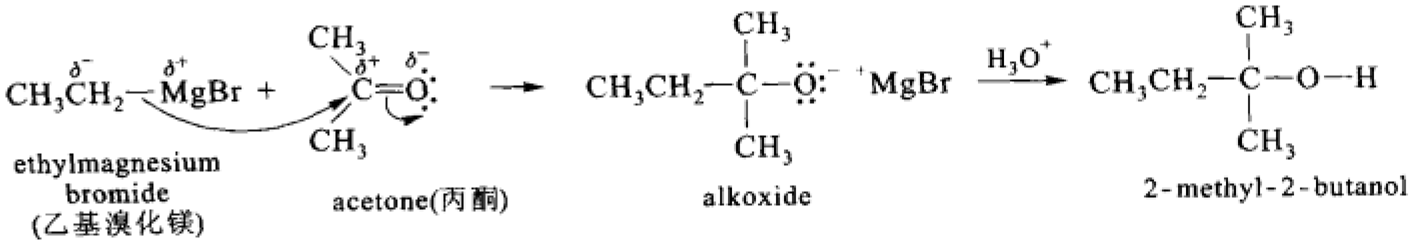
Ketones and aldehydes undergo many reactions to give a wide variety of useful derivatives. Their most common reactions is **nucleophilic addition**, addition of a nucleophile and a proton across the C=O double bond. The re-

activity of the carbonyl group arises from the electronegativity of the oxygen atom and the resulting polarization of the carbon-oxygen double bond. The electrophilic carbonyl carbon atom is sp^2 hybridized and flat, leaving it relatively unhindered and open to attack from either face of the double bond.

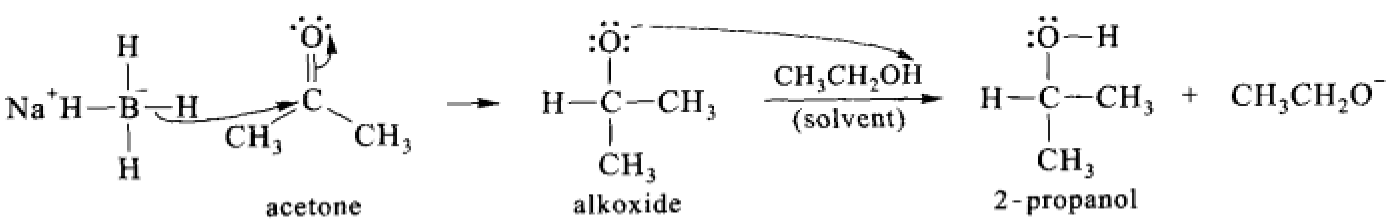
As a nucleophile attacks the carbonyl group, the carbon atom changes hybridization from sp^2 to sp^3. The electrons of the pi bond are forced out to the oxygen atom to form an alkoxide anion, which protonates to give the product of nucleophilic addition.



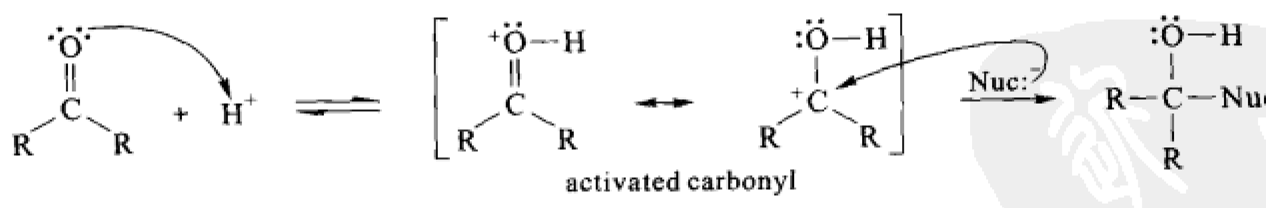
We have seen at least two examples of nucleophilic addition to ketones and aldehydes. A Grignard reagent (a strong nucleophile resembling a carbanion, R:⁻) attacks the electrophilic carbonyl atom to give an alkoxide intermediate. Subsequent protonation gives an alcohol.



Hydride reduction of a ketone or aldehyde is another example of nucleophilic addition, with hydride ion (H:⁻) serving as the nucleophile. Attack by hydride gives an alkoxide that protonates to form an alcohol.



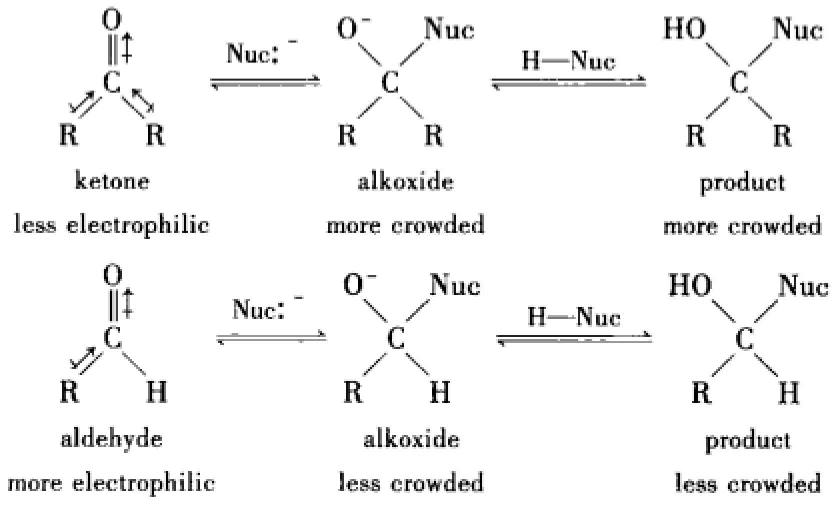
Weak nucleophiles, such as water and alcohols, can add to activated carbonyl groups under acidic conditions. A carbonyl group is a weak base, and it can become protonated in an acidic solution. A carbonyl group that is protonated (or bonded to some other electrophile) is strongly electrophilic, inviting attack by a weak nucleophile.



In effect, the base-catalyzed addition to a carbonyl group results from nucleophilic attack of a strong nucleophile followed by protonation. Acid-catalyzed addition begins with protonation, followed by the attack of a weaker nucleophile. Many additions are reversible, with the position of the equilibrium depending on the relative stabilities of the reactants and products.

In most cases, aldehydes are more reactive than ketones toward nucleophilic additions. They usually react more quickly than ketones, and the position of the equilibrium usually lies more toward the products than with ketones. We explain aldehydes' enhanced reactivity by noticing that an aldehyde has only one electron-donating alkyl group, making the aldehyde carbonyl group slightly more electron-poor and electrophilic (an *electronic*

effect). Also, an aldehyde has only one bulky alkyl group (compared with two in a ketones), leaving the carbonyl group more exposed toward nucleophilic attack. Especially with a bulky nucleophile, the product of attack on the aldehyde is less hindered than the product from the ketone (a *steric effect*).

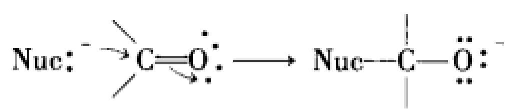


The following box summarizes the base-catalyzed and acid-catalyzed mechanisms for nucleophilic addition, together with their reverse reactions.

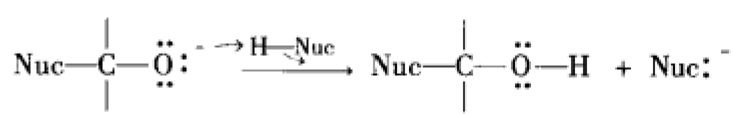
KEY MECHANISM 19-1 Nucleophilic Additions to Carbonyl Groups

Basic Conditions (*strong nucleophile*)

Step **1**: A strong nucleophile adds to the carbonyl group to form an alkoxide.

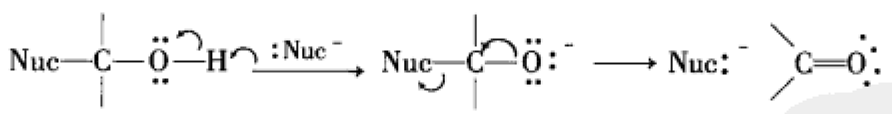


Step **2**: A weak acid protonates the alkoxide to give the addition product.



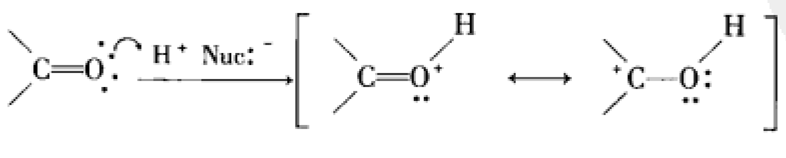
Reverse reaction: Deprotonation, followed by loss of the nucleophile.

Reverse reaction:

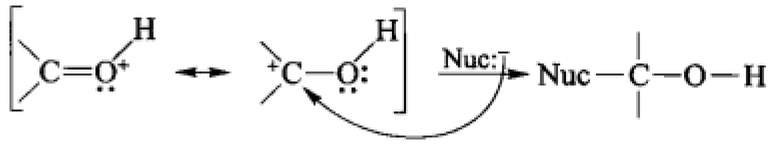


Acidic conditions (*weak nucleophile*, *activated carbonyl*)

Step **1**: Protonation activates the carbonyl group toward nucleophilic attack.

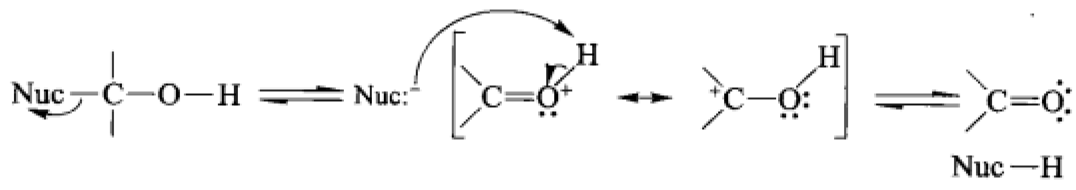


Step **2**: A weak nucleophile adds to the activated (protonated) carbonyl group.



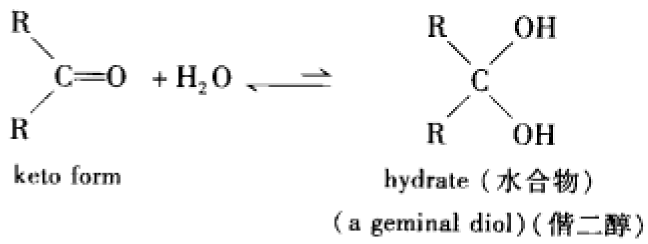
Reverse reaction: Loss of the weak nucleophile, followed by deprotonation.

Reverse reaction:



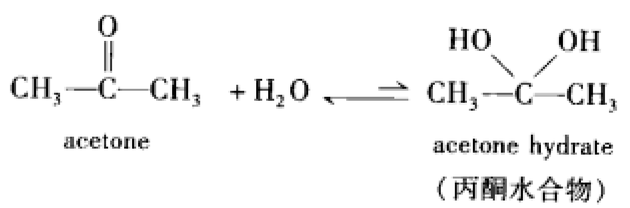
19-8 Hydration of Ketones and Aldehydes

In an aqueous solution, a ketone or an aldehyde is in equilibrium with its **hydrate**, a geminal diol. With most ketones, the equilibrium favors the unhydrated keto form of the carbonyl.



$$K = \frac{[\text{hydrate}]}{[\text{ketone}][H_2O]}$$

Example



$K = 0.002$

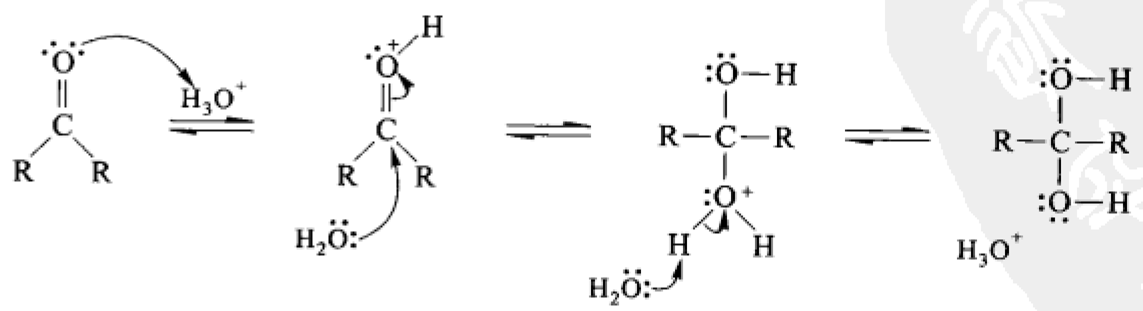
Hydration occurs through the nucleophilic addition mechanism, with water (in acid) or hydroxide ion (in base) serving as the nucleophile.

MECHANISM 19-2 Hydration of Ketones and Aldehydes

In acid

The acid-catalyzed hydration is a typical acid-catalyzed addition to the carbonyl group. Protonation, followed by addition of water, gives a protonated product. Deprotonation gives the hydrate.

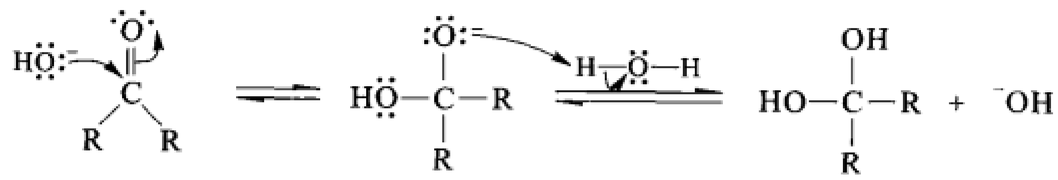
Step 1: Protonation. ***Step 2***: Water adds. ***Step 3***: Deprotonation.



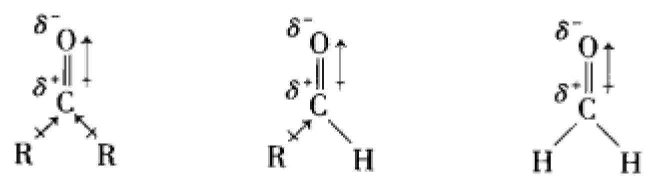
In base

The base-catalyzed hydration is a perfect example of base-catalyzed addition to a carbonyl group. The strong nucleophile adds, then protonation gives the hydrate.

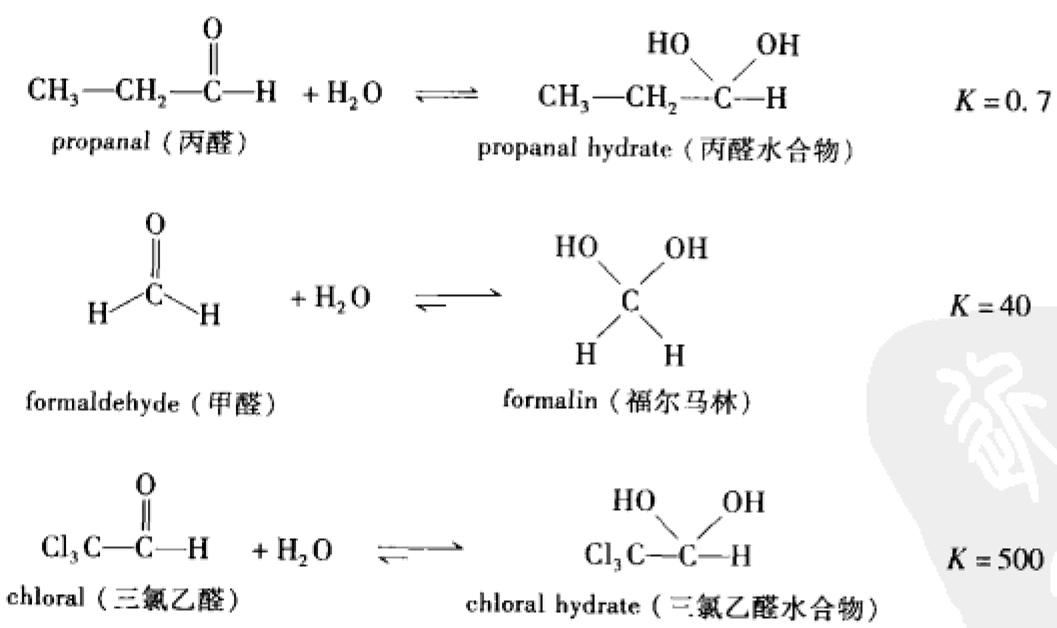
Step 1: Hydroxide adds. ***Step 2***: Protonation.



Aldehydes are more likely than ketones to form stable hydrates. The electrophilic carbonyl group of a ketone is stabilized by its two electron-donating alkyl groups, but an aldehyde carbonyl has only one stabilizing alkyl group; its partial positive charge is not as well stabilized. Aldehydes are thus *more electrophilic and less stable* than ketones. Formaldehyde, with no electron-donating groups, is even less stable than other aldehydes.



These stability effects are apparent in the equilibrium constants for hydration of ketones and aldehydes. Ketones have values of K_{eq} of about 10^{-4} to 10^{-2}. For most aldehydes, the equilibrium constant for hydration is close to 1. Formaldehyde, with no alkyl groups bonded to the carbonyl carbon, has a hydration equilibrium constant of about 40. Strongly electron-withdrawing substituents on the alkyl group of a ketone or aldehyde also destabilize the carbonyl group and favor the hydrate. Chloral (trichloroacetaldehyde) has an electron-withdrawing trichloromethyl group that favors the hydrate. Chloral forms a stable, crystalline hydrate that became famous in the movies as knockout drops or a Mickey Finn.



PROBLEM 19-7

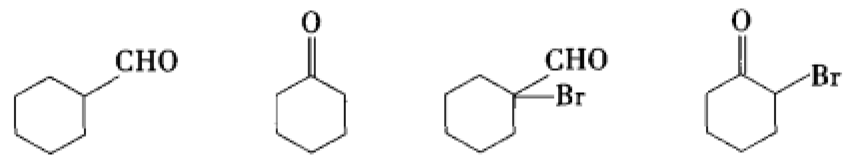
Propose mechanisms for

(a) The acid-catalyzed hydration of chloral to form chloral hydrate.

(b) The base-catalyzed hydration of acetone to form acetone hydrate.

PROBLEM 19-8

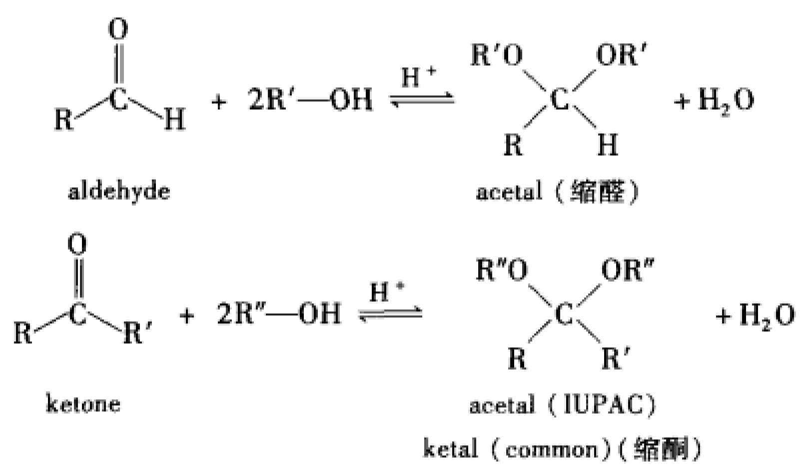
Rank the following compounds in order of increasing amount of hydrate present at equilibrium.



19-9 Formation of Acetals

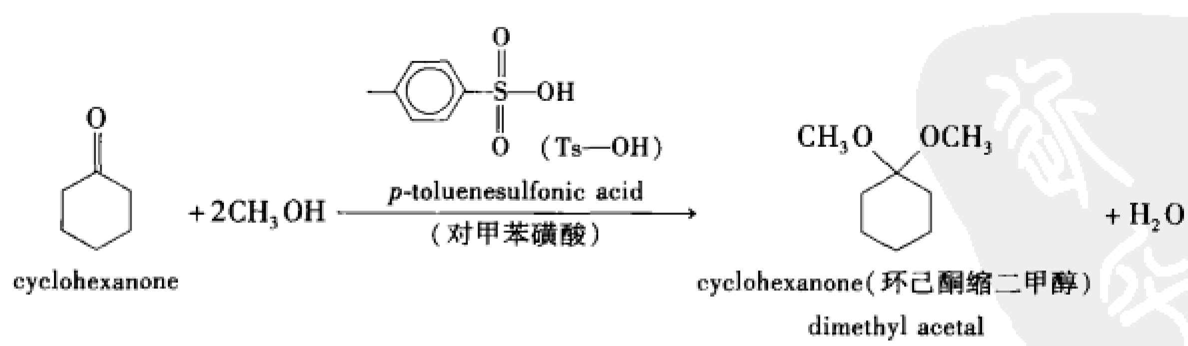
Just as ketones and aldehydes react with water to form hydrates, they also react with alcohols to form **acetals**. (Acetals formed from ketones are often called **ketals**, although this term has been dropped from the IUPAC nomenclature.) Acetals are some of the most common organic compounds in the world. Table sugar, cotton fabric, and a wooden ship are all composed of acetals.

In the formation of an acetal, two molecules of alcohol add to the carbonyl group, and one molecule of water is eliminated.



Although hydration is catalyzed by either acid or base, acetal formation must be acid-catalyzed. For example, consider the reaction of cyclohexanone with methanol, catalyzed by *p*-toluenesulfonic acid.

Overall reaction



The mechanism for this reaction follows. The first step is a typical acid-catalyzed addition to the carbonyl group. The acid catalyst protonates the carbonyl group, and the alcohol (a weak nucleophile) attacks the protonated, activated carbonyl. Loss of a proton from the positively charged intermediate gives a **hemiacetal**. The hemiacetal gets its name from the Greek prefix *hemi*-, meaning "half." Having added one molecule of the alcohol, the hemiacetal is halfway to becoming a "full" acetal. Like the hydrates of ketones and aldehydes, most hemiacetals are too unstable to be isolated and purified.

The second half of the mechanism converts the hemiacetal to the more stable acetal. Protonation of the hy-

droxyl group, followed by loss of water, gives a resonance-stabilized carbocation. Attack on the carbocation by methanol, followed by loss of a proton, gives the acetal.

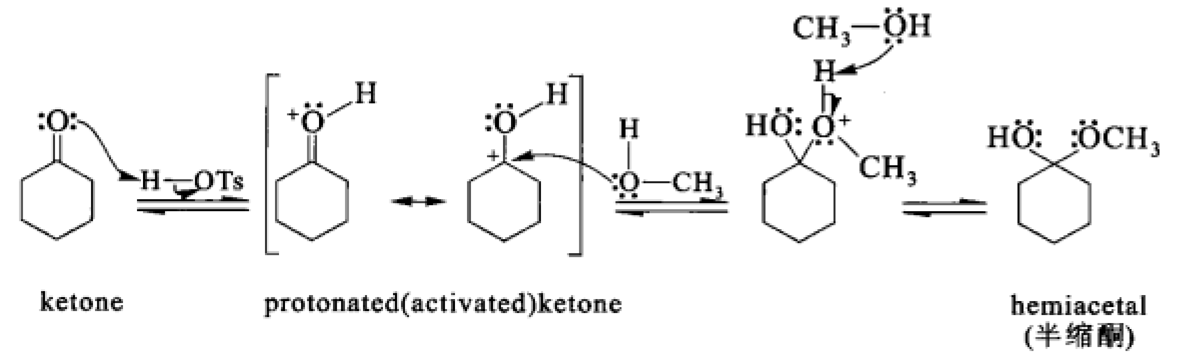
KEY MECHANISM 19-3 Formation of Acetals

Like imine formation, acetal formation is easily remembered by dividing it into two simple processes:

1. The first half is an acid-catalyzed addition of the alcohol to the carbonyl group.
2. The second half begins like an acid-catalyzed dehydration, but then another alcohol adds.

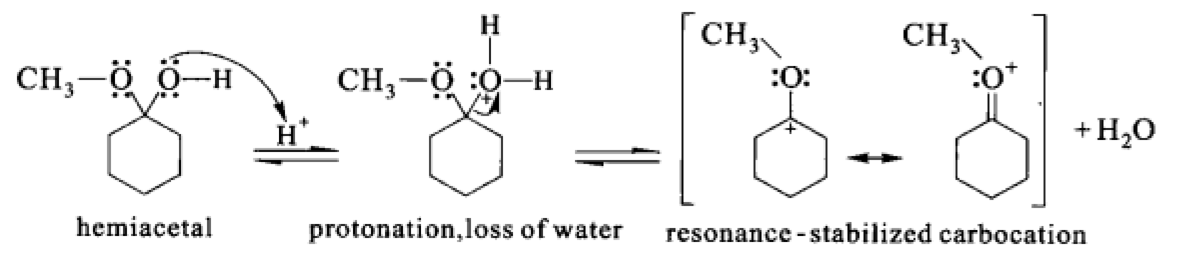
First part: Acid-catalyzed addition of the alcohol to the carbonyl group.

Step 1: Protonation. ***Step 2***: Alcohol adds. ***Step 3***: Deprotonation.

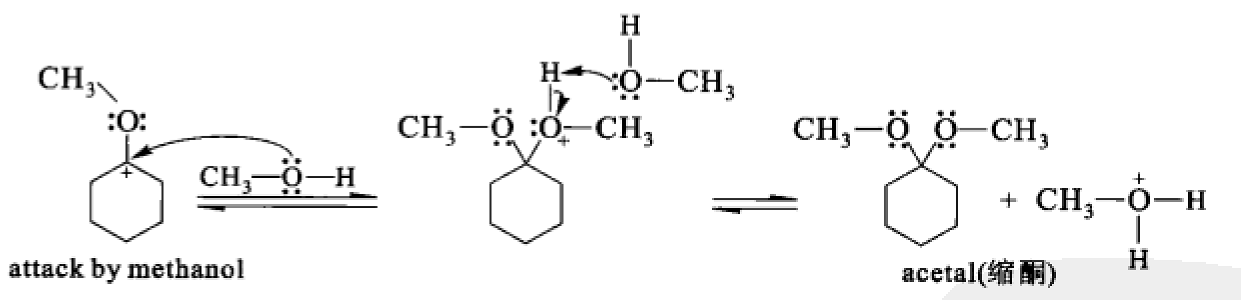


The second half begins like an acid-catalyzed dehydration

Step 4: Protonation. ***Step 5***: Loss of water.



Step 6: Second alcohol adds. ***Step 7***: Deprotonation.



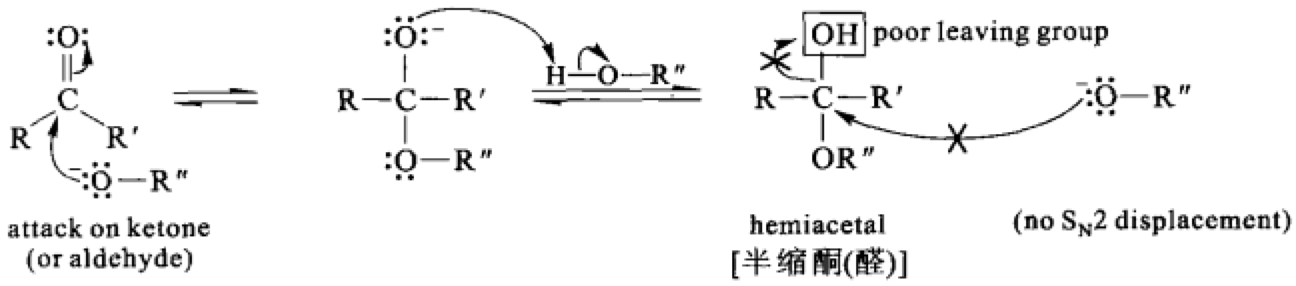
PROBLEM 19-9

Propose a mechanism for the acid-catalyzed reaction of benzaldehyde with methanol to give benzaldehyde dimethyl acetal.

Since hydration is catalyzed by either acid or base, you might wonder why acetal formation is catalyzed only by acid. In fact, the first step (formation of the hemiacetal) can be base-catalyzed, involving attack by alkoxide ion and protonation of the alkoxide. The second step requires replacement of the hemiacetal —OH group by the alcohol —OR″ group. Hydroxide ion is a poor leaving group for the S_N2 reaction, so alkoxide cannot displace the

—OH group. This replacement occurs under acidic conditions, however, because protonation of the —OH group and loss of water gives a resonance-stabilized cation.

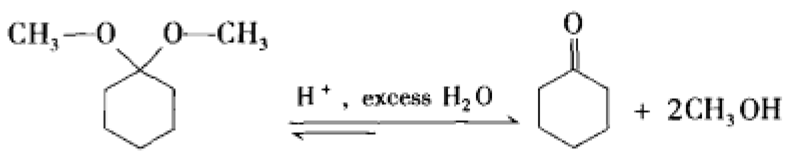
Attempted base-catalyzed acetal formation



Equilibrium of Acetal Formation Acetal formation is reversible, and the equilibrium constant determines the proportions of reactants and products present at equilibrium. For simple aldehydes, the equilibrium constants generally favor the acetal products. For example, the acid-catalyzed reaction of acetaldehyde with ethanol gives a good yield of the acetal.

With hindered aldehydes and with most ketones, the equilibrium constants favor the carbonyl compounds rather than the acetals. To enhance these reactions, the alcohol is often used as the solvent to assure a large excess. The water formed as a byproduct is removed by distillation to force the equilibrium toward the right.

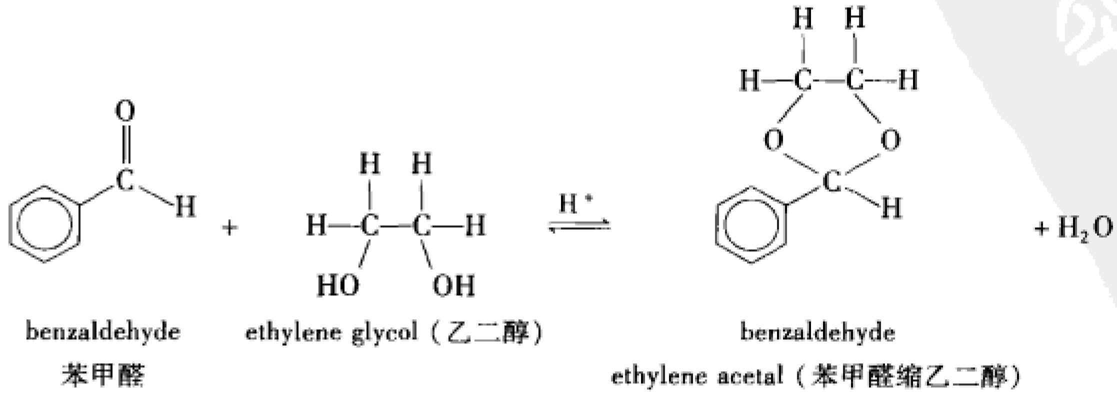
Conversely, most acetals are hydrolyzed simply by shaking them with dilute acid in water. The large excess of water drives the equilibrium toward the ketone or aldehyde. The mechanism is simply the reverse of acetal formation. For example, cyclohexanone dimethyl acetal is quantitatively hydrolyzed to cyclohexanone by brief treatment with dilute aqueous acid.

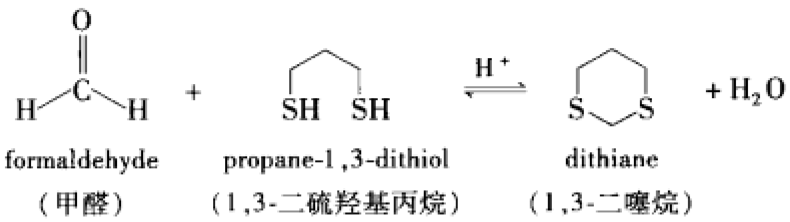


PROBLEM 19-10

Propose a mechanism for the acid-catalyzed hydrolysis of cyclohexanone dimethyl acetal.

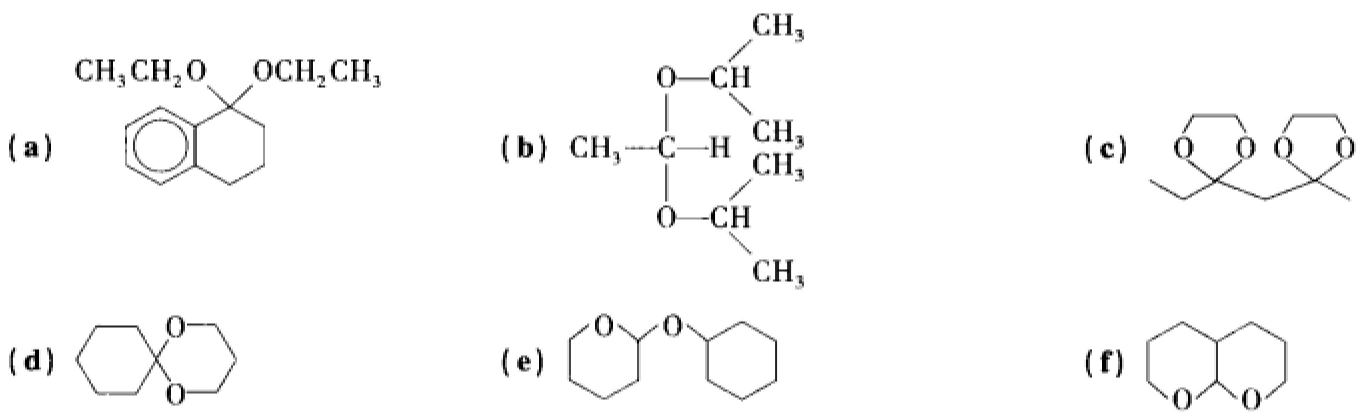
Cyclic Acetals Formation of an acetal using a diol as the alcohol gives a cyclic acetal. Cyclic acetals often have more favorable equilibrium constants, since there is a smaller entropy loss when two molecules (a ketone and a diol) condense than when three molecules (a ketone and two molecules of an alcohol) condense. Ethylene glycol is often used to make cyclic acetals; its acetals are called **ethylene acetals** (or **ethylene ketals**). Dithiane and its alkylated derivatives are examples of cyclic thioacetals (sulfur acetals).





PROBLEM 19-11

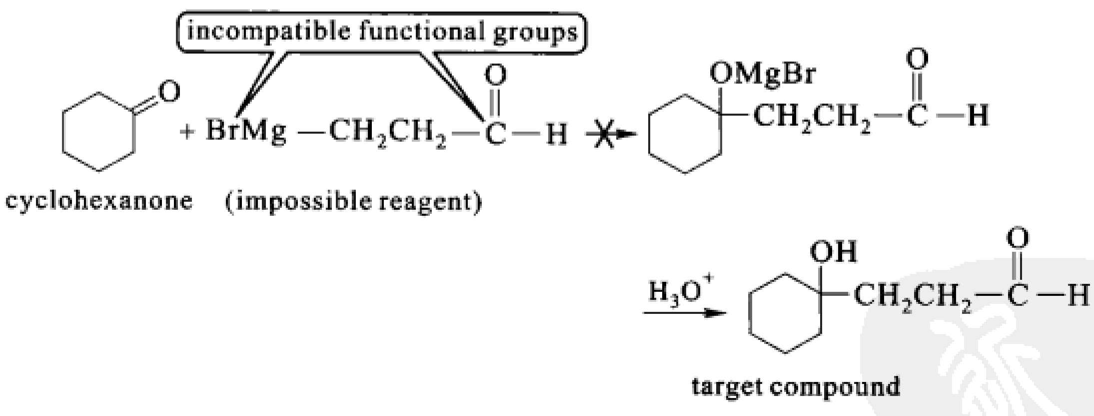
Show what alcohols and carbonyl compounds give the following derivatives.



Use of Acetals as Protecting Groups Acetals hydrolyze under acidic conditions, but they are stable to strong bases and nucleophiles. Acetals are easily made from the corresponding ketones and aldehydes and easily converted back to the parent carbonyl compounds. This easy interconversion makes acetals attractive as **protecting groups** to prevent ketones and aldehydes from reacting with strong bases and nucleophiles.

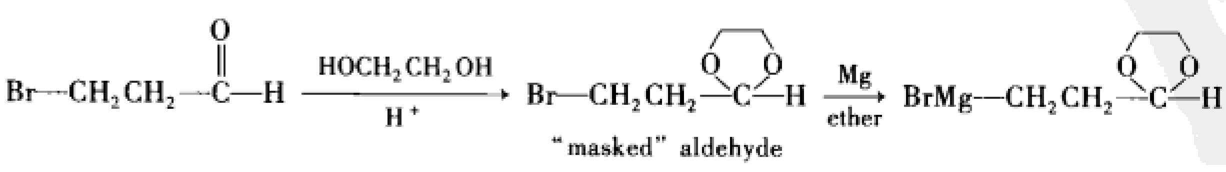
As an example, consider the following proposed synthesis. The necessary Grignard reagent could not be made because the carbonyl group would react with the nucleophilic organometallic group.

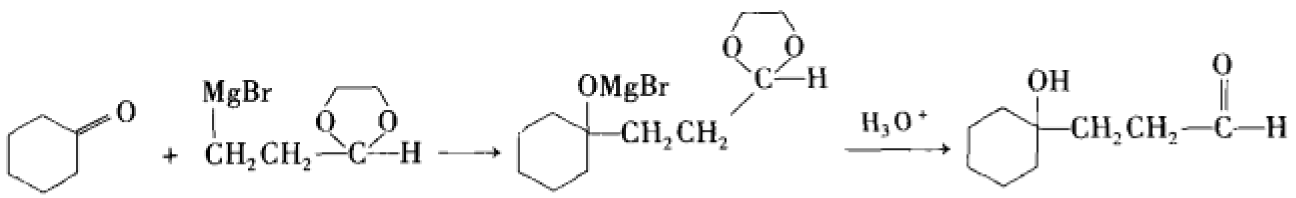
Proposed synthesis



If the aldehyde is protected as an acetal, however, it is unreactive toward a Grignard reagent. The "masked" aldehyde is converted to the Grignard reagent, which is allowed to react with cyclohexanone. Dilute aqueous acid both protonates the alkoxide to give the alcohol and hydrolyzes the acetal to give the deprotected aldehyde.

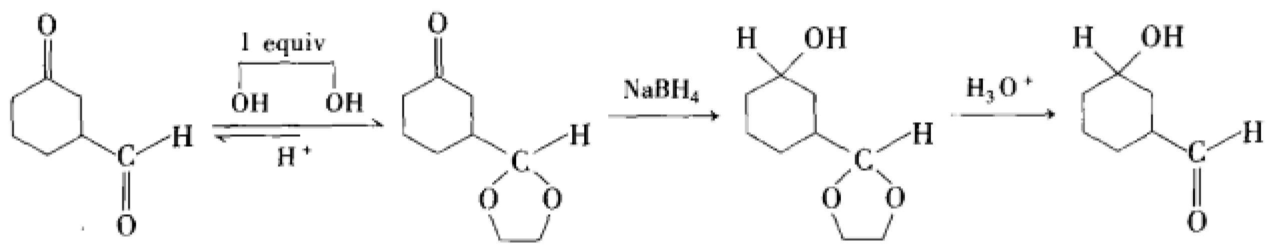
Actual synthesis





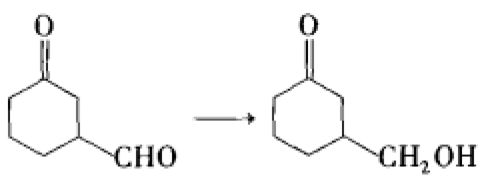
target compound

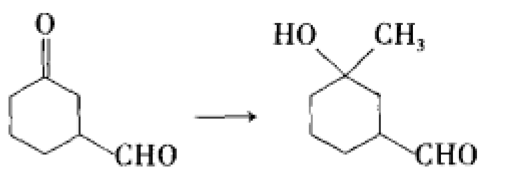
Selective Acetal Formation Because aldehydes form acetals more readily than ketones, we can protect an aldehyde selectively in the presence of a ketone. This selective protection leaves the ketone available for modification under neutral or basic conditions without disturbing the more reactive aldehyde group. The following example shows the reduction of a ketone in the presence of a more reactive aldehyde:

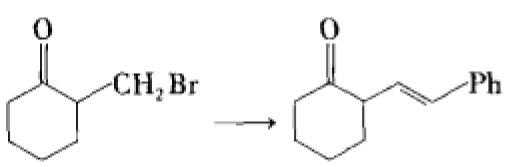


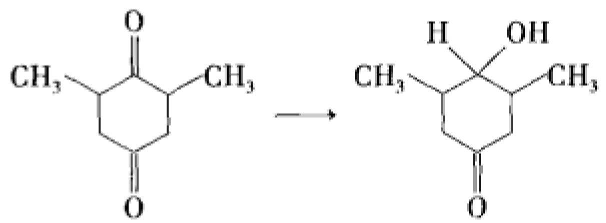
PROBLEM 19-12

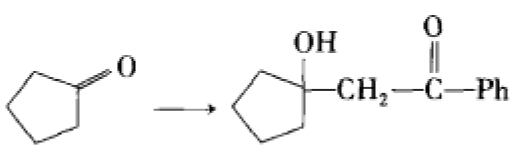
Show how you would accomplish the following syntheses. You may use whatever additional reagents you need.

(a) 

(b) 

(c) 

(d) 

(e) 

(f) $BrCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow HC{\equiv}CCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

19-10 Formation of Cyanohydrins

Hydrogen cyanide (H—C≡N) is a toxic, water-soluble liquid that boils at 26 ℃. Because it is mildly acidic, HCN is sometimes called hydrocyanic acid.

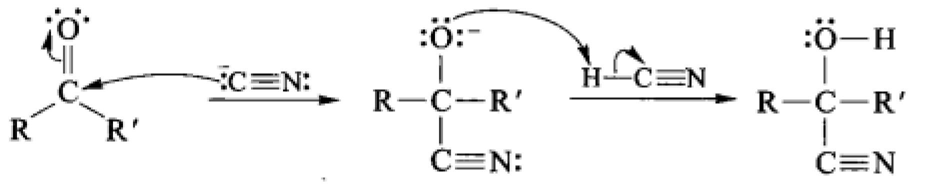
$$H{-}C{\equiv}N{:} + H_2O \rightleftharpoons H_3O^+ + {}^-{:}C{\equiv}N{:} \qquad pK_a = 9.2$$

The conjugate base of hydrogen cyanide is the cyanide ion($^-$:C≡N:). Cyanide ion is a strong base and a strong nucleophile. It attacks ketones and aldehydes to give addition products called **cyanohydrins**. The mechanism is a base-catalyzed nucleophilic addition: attack by cyanide ion on the carbonyl group, followed by protonation of the intermediate.

MECHANISM 19-4 Formation of Cyanohydrins

Cyanohydrin formation is a perfect example of base-catalyzed addition to a carbonyl group. The strong nucleophile adds in the first step to give an alkoxide. Protonation gives the cyanohydrin.

Step 1: Cyanide adds to the carbonyl. ***Step 2***: Protonation gives the cyanohydrin.



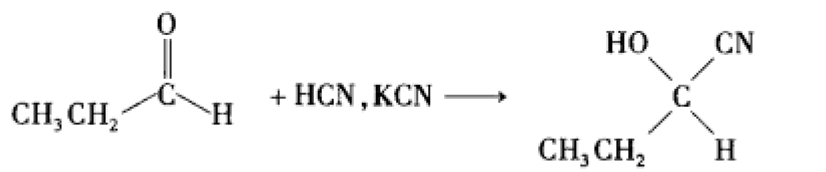
ketone or aldehyde intermediate cyanohydrin(α-羟基腈)

Cyanohydrins may be formed using liquid HCN with a catalytic amount of sodium cyanide or potassium cyanide. HCN is highly toxic and volatile, however, and therefore dangerous to handle. Many procedures use a full equivalent of sodium or potassium cyanide (rather than HCN), dissolved in some other proton-donating solvent.

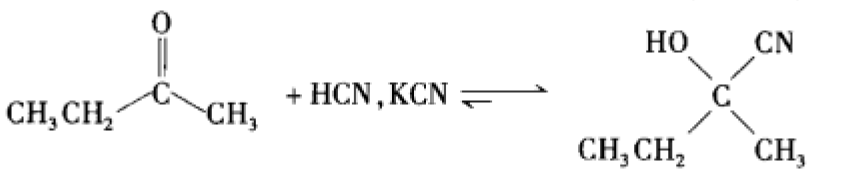
Cyanohydrin formation is reversible, and the equilibrium constant may or may not favor the cyanohydrin. These equilibrium constants follow the general reactivity trend of ketones and aldehydes:

formaldehyde > other aldehydes > ketones

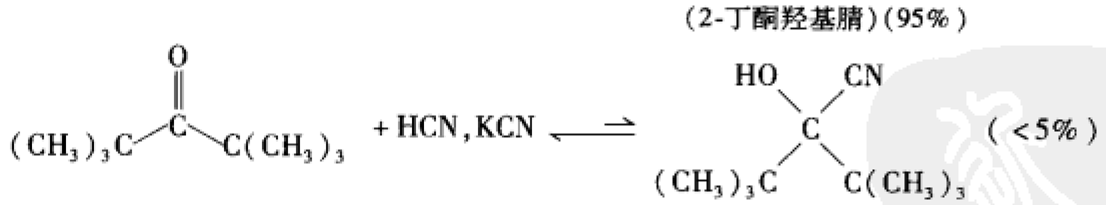
Formaldehyde reacts quickly and quantitatively with HCN. Most other aldehydes have equilibrium constants that favor cyanohydrin formation. Reactions of HCN with ketones have equilibrium constants that may favor either the ketones or the cyanohydrins, depending on the structure. Ketones that are hindered by large alkyl groups react slowly with HCN and give poor yields of cyanohydrins.



propanal propanal cyanohydrin (丙醛羟基腈)(100%)



2-butanone 2-butanone cyanohydrin (2-丁酮羟基腈)(95%)



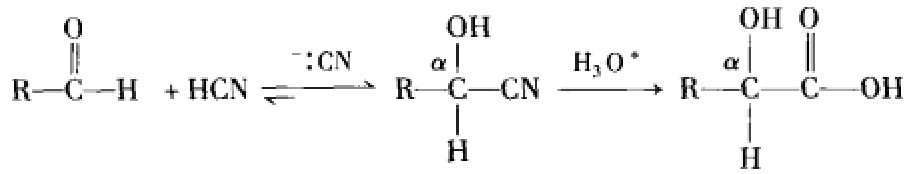
di-*t*-butyl ketone slow reaction, poor yields

The failure with bulky ketones is largely due to steric effects. Cyanohydrin formation involves rehybri-dizing the sp^2 carbonyl carbon to sp^3, narrowing the angle between the alkyl groups from about 120° to about 109.5°, increasing their steric interference.

PROBLEM 19-13

Propose a mechanism for each cyanohydrin synthesis just shown.

Organic compounds containing the cyano group (—C≡N) are called **nitriles**. A cyanohydrin is therefore an α-hydroxynitrile. Nitriles hydrolyze to carboxylic acids under acidic conditions, so cyanohydrins hydrolyze to α-hydroxy acids. This is the most convenient method for making many α-hydroxy acids.



aldehyde　　cyanohydrin (α-羟基腈)　　α-hydroxy acid (α-羟基酸)

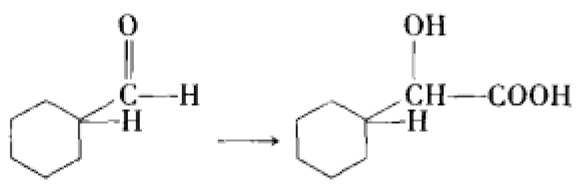
PROBLEM 19-14

Show how you would accomplish the following syntheses.

(a) acetophenone → acetophenone cyanohydrin

(b) 1-hexanol → hexanal cyanohydrin

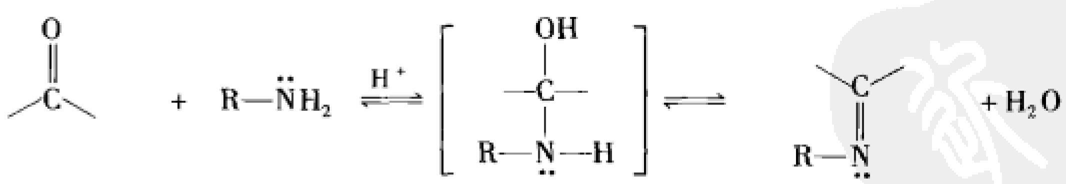
(c)



19-11 Formation of Imines

Under the proper conditions, either ammonia or a primary amine reacts with a ketone or an aldehyde to form an **imine**. Imines are nitrogen analogues of ketones and aldehydes, with a carbon-nitrogen double bond in place of the carbonyl group. Imines are commonly involved as synthetic intermediates, both in biosynthesis and in industrial synthesis. One of the best methods for making amines (both in organisms and in the lab) involves making an imine, then reducing it to the amine.

Like amines, imines are basic; a substituted imine is also called a **Schiff base**. Imine formation is an example of a large class of reactions called **condensations**, reactions in which two (or more) organic compounds are joined, often with the loss of water or another small molecule.



ketone or aldehyde　　primary amine　　carbinolamine (醇胺)　　imine (Schiff base) (亚胺,又称席夫碱)

The mechanism of imine formation (Key Mechanism 19-5) begins with an acidcatalyzed nucleophilic addition of the amine to the carbonyl group. Attack by the amine, followed by deprotonation of the nitrogen atom, gives an unstable intermediate called a **carbinolamine**.

A carbinolamine converts to an imine by losing water and forming a double bond: a dehydration. This dehydration follows the same mechanism as the acid-catalyzed dehydration of an alcohol. Protonation of the hydroxyl group converts it to a good leaving group, and it leaves as water. The resulting cation is stabilized by a resonance

structure, with all octets filled and the positive charge on nitrogen. Loss of a proton gives the imine.

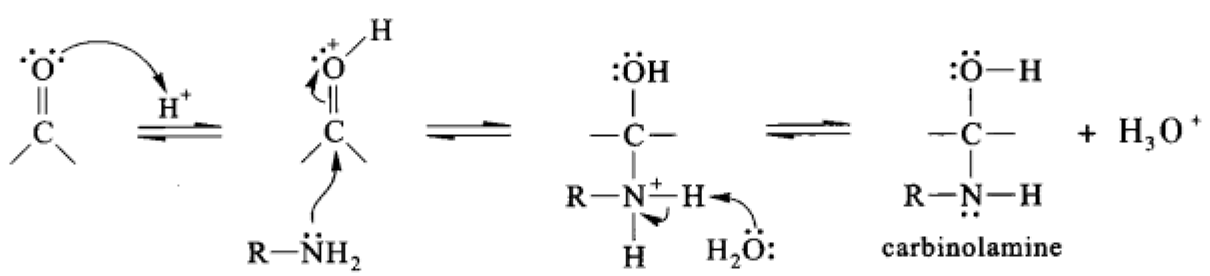
KEY MECHANISM 19-5 Formation of Imines

This mechanism is more easily remembered by dividing it into two parts:

1. Acid-catalyzed addition of the amine to the carbonyl group.
2. Acid-catalyzed dehydration.

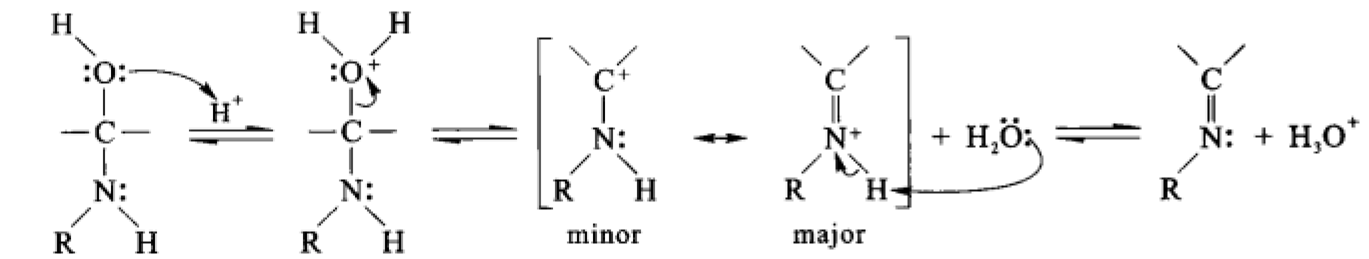
First part: Acid-catalyzed addition of the amine to the carbonyl group.

Step 1: Protonation of the carbonyl. ***Step 2***: Addition of the amine. ***Step 3***: Deprotonation



Second part: Acid-catalyzed dehydration.

Step 4: Protonation of the —OH group. ***Step 5***: Loss of H_2O. ***Step 6***: Deprotonation.



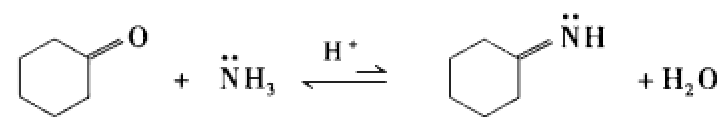
PROBLEM 19-15

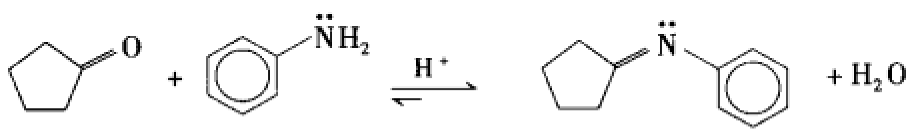
(a) What would happen if the reaction were made too acidic by the addition of too much acid?

(b) What would happen if it were too basic?

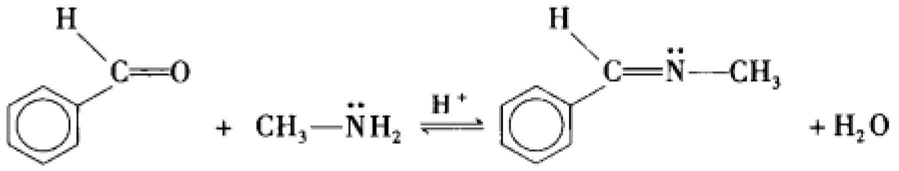
The proper pH is crucial to imine formation. The second half of the mechanism is acid-catalyzed, so the solution must be somewhat acidic. If the solution is too acidic, however, the amine becomes protonated and nonnucleophilic, inhibiting the first step. Figure 19-1 shows that the rate of imine formation is fastest around pH 4.5.

The following equations show some typical imine-forming reactions. In each case, notice that the C=O group of the ketone or aldehyde is replaced by the C=N—R group of the imine.





cyclopentanone   aniline (苯胺)   cyclopentanone phenyl imine (*N*-苯基环戊酮亚胺)



benzaldehyde   methylamine   benzaldehyde methyl imine (*N*-甲基苯甲醛亚胺)

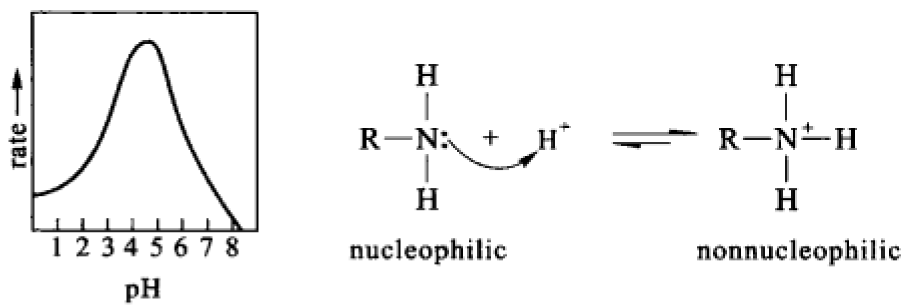


Figure 19−1 Although dehydration of the carbinolamine is acid-catalyzed, excess acid stops the first step by protonating the amine. Formation of the imine is fastest around pH 4.5.

PROBLEM 19−16

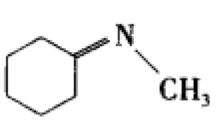
Propose mechanisms for the three imine-forming reactions just shown.

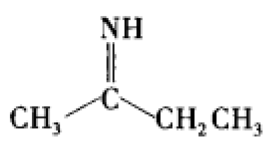
PROBLEM 19−17

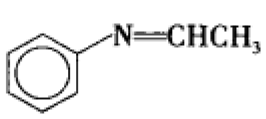
Depending on the reaction conditions, two different imines of formula C_8H_9N might be formed by the reaction of benzaldehyde with methylamine. Explain, and give the structures of the two imines.

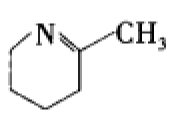
PROBLEM 19−18

Give the structures of the carbonyl compound and the amine used to form the following imines.

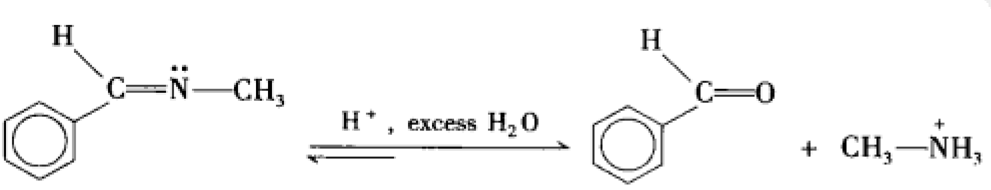
(a) 

(b) 

(c) 

(d) 

Imine formation is reversible, and most imines can be hydrolyzed back to the amine and the ketone or aldehyde. The principle of microscopic reversibility states that the reverse reaction taking place under the same conditions should follow the same pathway but in reverse order. Therefore, the mechanism for hydrolysis of an imine is simply the reverse of the mechanism for its formation.

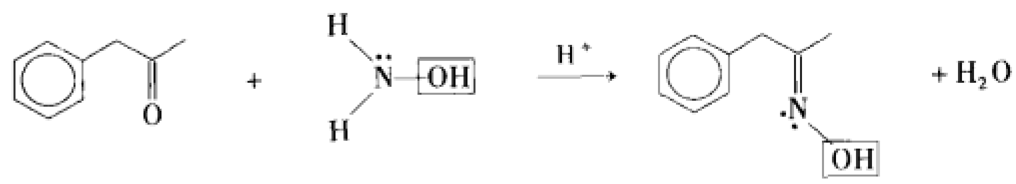


PROBLEM 19−19

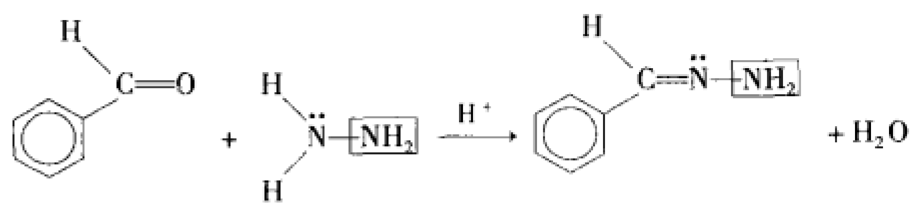
Propose a mechanism for the hydrolysis of benzaldehyde methyl imine just show.

19−12 Condensations with Hydroxylamine and Hydrazines

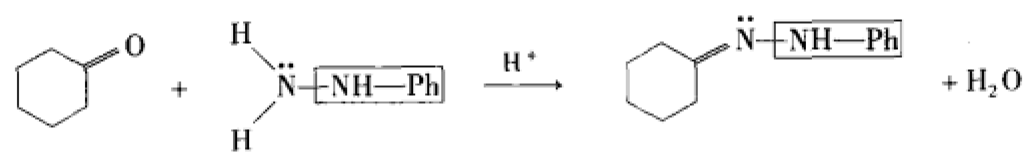
Ketones and aldehydes also condense with other ammonia derivatives, such as hydroxylamine and substituted hydrazines, to give imine derivatives. The equilibrium constants for these reactions are usually more favorable than for reactions with simple amines. Hydroxylamine reacts with ketones and aldehydes to form **oximes**; hydrazine derivatives react to form **hydrazones**; and semicarbazide reacts to form **semicarbazones**. The mechanisms of these reactions are similar to the mechanism of imine formation.



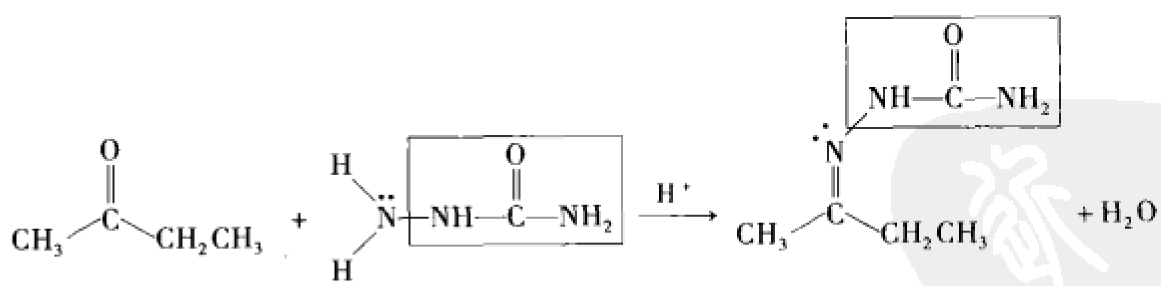
phenyl-2-propanone hydroxylamine（羟胺） phenyl-2-propanone oxime（苯基−2−丙酮肟）



benzaldehyde hydrazine（肼） benzaldehyde hydrazone（苯甲醛腙）



cyclohexanone phenylhydrazine（苯肼） cyclohexanone phenylhydrazone（环己酮苯腙）



2-butanone semicarbazide（氨基脲） 2-butanone（2−丁酮缩氨脲）semicarbazone

These derivatives are useful both as starting materials for further reactions and for characterization and identification of the original carbonyl compounds. Oximes, semicarbazones, and phenylhydrazones are often solid compounds with characteristic melting points. Standard tables give the melting points of these derivatives for thousands of different ketones and aldehydes.

If an unknown compound forms one of these derivatives, the melting point can be compared with that in the table. If the compound's physical properties match those of a known compound and the melting point of its ox-

ime, semicarbazide, or phenylhydrazone matches as well, we can be fairly certain of a correct identification.

SUMMARY Condensations of Amines with Ketones and Aldehydes

$$\gt C{=}O + H_2\ddot{N}{-}\boxed{Z} \xrightarrow{H^+} \gt C{=}\ddot{N}{-}\boxed{Z} + H_2O$$

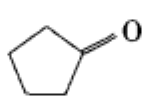
Z in Z—NH₂	*Reagent*	*Product*
—H	$H_2\ddot{N}{-}\boxed{H}$ ammonia 氨	$\gt C{=}\ddot{N}{-}\boxed{H}$ an imine 亚胺
—R	$H_2\ddot{N}{-}\boxed{R}$ primary amine 伯胺	$\gt C{=}\ddot{N}{-}\boxed{R}$ an imine (Schiff base) 亚胺(席夫碱)
—OH	$H_2\ddot{N}{-}\boxed{OH}$ hydroxylamine 羟胺	$\gt C{=}\ddot{N}{-}\boxed{OH}$ an oxime 肟
$—NH_2$	$H_2\ddot{N}{-}\boxed{NH_2}$ hydrazine 肼	$\gt C{=}\ddot{N}{-}\boxed{NH_2}$ a hydrazone 腙
—NHPh	$H_2\ddot{N}{-}\boxed{NHPh}$ phenylhydrazine 苯肼	$\gt C{=}\ddot{N}{-}\boxed{NHPh}$ a phenylhydrazone 苯腙
$—NH\overset{O}{\overset{\Vert}{C}}NH_2$	$H_2\ddot{N}{-}\boxed{NH{-}\overset{O}{\overset{\Vert}{C}}{-}NH_2}$ 氨基脲 semicarbazide	$\gt C{=}\ddot{N}{-}\boxed{NH{-}\overset{O}{\overset{\Vert}{C}}{-}NH_2}$ 缩氨脲 a semicarbazone

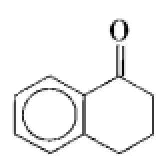
PROBLEM 19-20

2,4-Dinitrophenylhydrazine is frequently used for making derivatives of ketones and aldehydes because the products (2,4-dinitrophenylhydrazones, called **2,4-DNP derivatives**) are even more likely than the phenylhydrazones to be solids with sharp melting points. Propose a mechanism for the reaction of acetone with 2,4-dinitrophenylhydrazine in a mildly acidic solution.

PROBLEM 19-21

Predict the products of the following reactions.

(a)  $+ \ HO{-}NH_2 \xrightarrow{H^+}$

(b)  $+ \ H_2N{-}NH_2 \xrightarrow{H^+}$

(c) $Ph{-}CH{=}CH{-}CHO + H_2N{-}\overset{O}{\overset{\Vert}{C}}{-}NH{-}NH_2 \xrightarrow{H^+}$

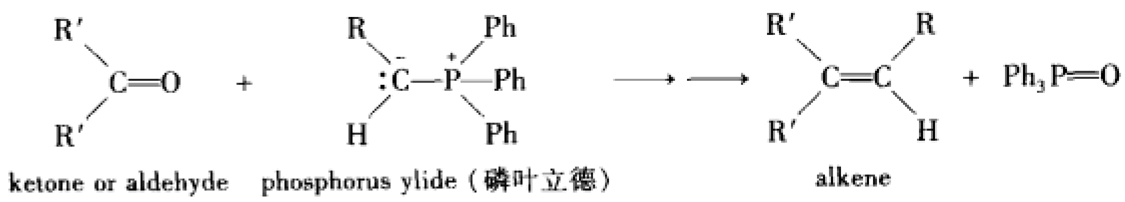
(d) $Ph{-}\overset{O}{\overset{\Vert}{C}}{-}Ph + Ph{-}NH{-}NH_2 \xrightarrow{H^+}$

19-13 The Wittig Reaction

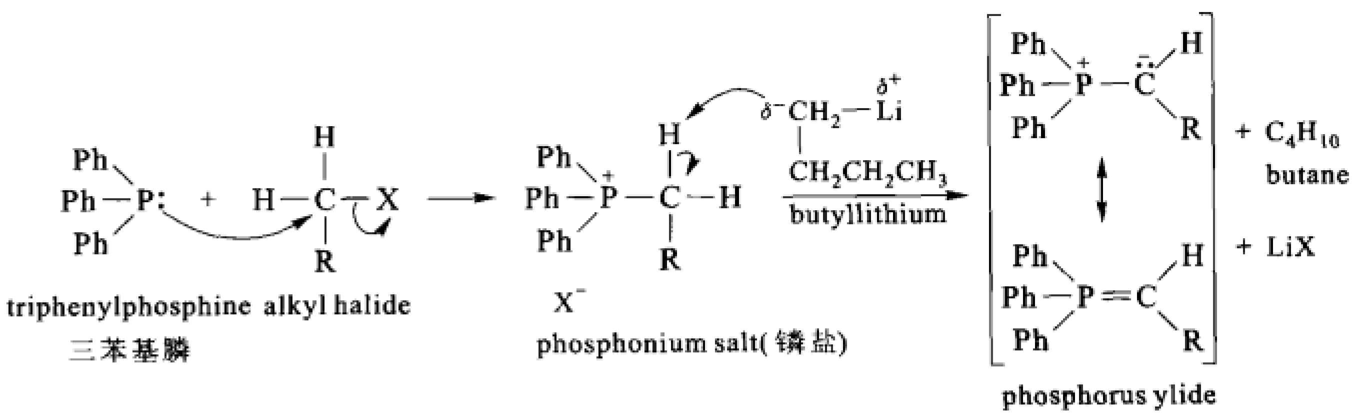
We have seen carbonyl groups undergo addition by a variety of carbanion-like reagents, including Grignard reagents, organolithium reagents, and acetylide ions. In 1954, Georg Wittig discovered a way of adding a phosphorus-stabilized carbanion to a ketone or aldehyde. The product is not an alcohol, howe-ver, because the intermedi-

ate undergoes elimination to an alkene. In effect, the **Wittig reaction** converts the carbonyl group of a ketone or an aldehyde into a new C=C double bond where no bond existed before. This reaction proved so useful that Wittig received the Nobel Prize in chemistry in 1979 for this discovery.

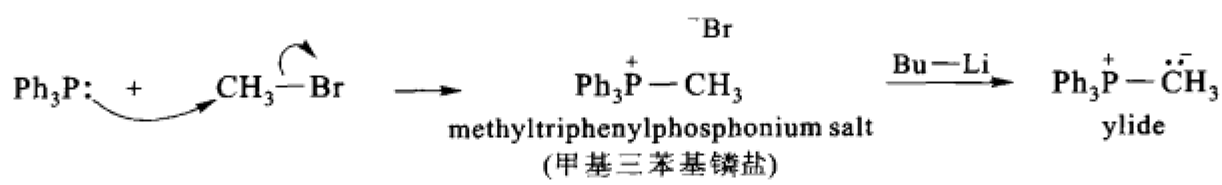
The Wittig reaction



The phosphorus-stabilized carbanion is an **ylide** (pronounced "ill'-id")—a molecule that bears no overall charge but has a negatively charged carbon atom bonded to a positively charged heteroatom. Phosphorus ylides are prepared from triphenylphosphine and alkyl halides in a two-step process. The first step is nucleophilic attack by triphenylphosphine on an unhindered (usually primary) alkyl halide. The product is an alkyltriphenylphosphonium salt. The phosphonium salt is treated with a strong base (usually butyllithium) to abstract a proton from the carbon atom bonded to phosphorus.



Examples



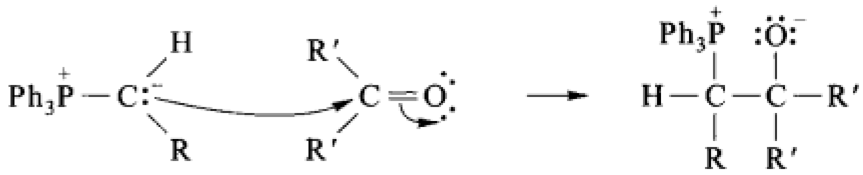
The phosphorus ylide has two resonance forms: one with a double bond between carbon and phosphorus, and another with charges on carbon and phosphorus. The double-bonded resonance form requires ten electrons in the valence shell of phosphorus, using a *d* orbital. The pi bond between carbon and phosphorus is weak, and the charged structure is the major contributor. The carbon atom actually bears a partial negative charge, balanced by a corresponding positive charge on phosphorus.

Because of its carbanion character, the ylide carbon atom is strongly nucleophilic. It attacks a carbonyl group to give a charge-separated intermediate called a *betaine* (pronounced "bay'-tuh-ene"). A betaine is an unusual compound because it contains a negatively charged oxygen and a positively charged phosphorus on adjacent carbon atoms. Phosphorus and oxygen form strong bonds, and the attraction of opposite charges promotes the fast formation of a four-membered *oxaphosphetane* ring. (In some cases, the oxaphosphetane may be formed directly by a cycloaddition, rather than via a betaine.)

The four-membered ring quickly collapses to give the alkene and triphenylphosphine oxide. Triphenylphosphine oxide is exceptionally stable, and the conversion of triphenylphosphine to triphenylphosphine oxide provides the driving force for the Wittig reaction.

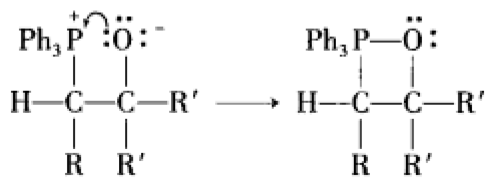
MECHANISM 19-6 The Wittig Reaction

Step 1 : The ylide attacks the carbonyl to form a betaine.



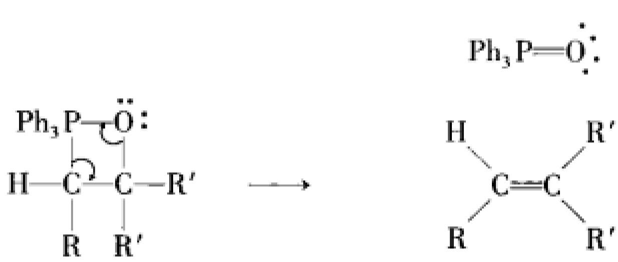
ylide ketone or aldehyde a betaine(内盐)

Step 2 : The betaine closes to a four-membered ring oxaphosphetane (first P—O bond formed).



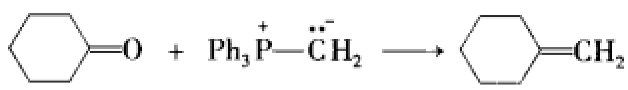
a betaine oxaphosphetane

Step 3 : The ring collapses to the products (second P—O bond formed).

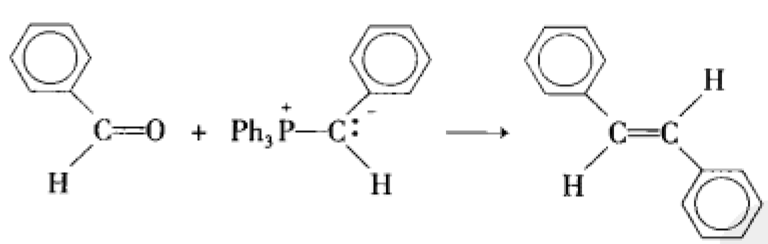


four-membered ring triphenylphosphine oxide(三苯氧膦) + alkene

The following examples show the formation of carbon-carbon double bonds using the Wittig reaction. Mixtures of cis and trans isomers often result when geometric isomerism is possible.



85%



PROBLEM 19-22

Trimethylphosphine is much less expensive than triphenylphosphine. Why is trimethylphosphine unsuitable for making most phosphorus ylides?

PROBLEM 19-23

Like other strong nucleophiles, triphenylphosphine attacks and opens epoxides. The initial product (a betaine) quickly cyclizes to an oxaphosphetane that collapses to an alkene and triphenylphosphine oxide.

(a) Show each step in the reaction of *trans*-2,3-epoxybutane with triphenylphosphine to give 2-butene. What is the stereochemistry of the double bond in the product?

(b) Show how this reaction might be used to convert *cis*-cyclooctene to *trans*-cyclooctene.

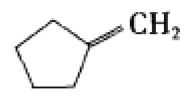
PROBLEM 19–24

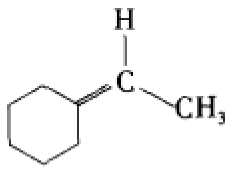
Show how Witting reactions might be used to synthesize the following compounds. In each case, start with an alkyl halide and a ketone or an aldehyde.

(**a**) $Ph—CH{=}C(CH_3)_2$

(**b**) $Ph—C(CH_3){=}CH_2$

(**c**) $Ph—CH{=}CH—CH{=}CH—Ph$

(**d**) 

(**e**) 

19–14 Oxidation of Aldehydes

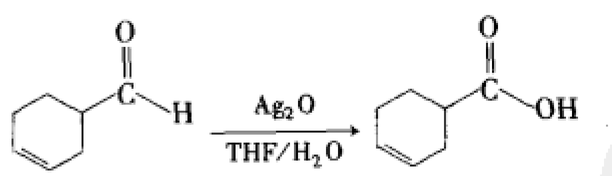
Unlike ketones, aldehydes are easily oxidized to carboxylic acids by common oxidants such as chromic acid, chromium trioxide, permanganate, and peroxy acids. Aldehydes oxidize so easily that air must be excluded from their containers to avoid slow oxidation by atmospheric oxygen. Because aldehydes oxidize so easily, mild reagents such as Ag_2O can oxidize them selectively in the presence of other oxidizable functional groups.

$$R—\overset{O}{\overset{\|}{C}}—H \xrightarrow[\text{(oxidizing agent)}]{[O]} R—\overset{O}{\overset{\|}{C}}—OH$$

Examples

$$CH_3—\underset{CH_3}{\underset{|}{CH}}—\overset{O}{\overset{\|}{C}}—H \xrightarrow[\text{dil. } H_2SO_4]{Na_2Cr_2O_7} CH_3—\underset{CH_3}{\underset{|}{CH}}—\overset{O}{\overset{\|}{C}}—OH$$

isobutyraldehyde isobutyric acid (90%)



(97%)

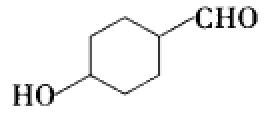
Silver ion, Ag^+, oxidizes aldehydes selectively in a convenient functional-group test for aldehydes. The **Tollens test** involves adding a solution of silver-ammonia complex (the **Tollens reagent**) to the unknown compound. If an aldehyde is present, its oxidation reduces silver ion to metallic silver in the form of a black suspension or a silver mirror deposited on the inside of the container. Simple hydrocarbons, ethers, ketones, and even alcohols do not react with the Tollens reagent.

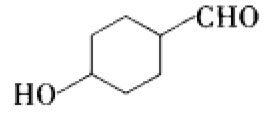
$$R—\overset{O}{\overset{\|}{C}}—H + 2\,\overset{+}{Ag}(NH_3)_2 + 3\,^{-}OH \xrightarrow{H_2O} 2Ag\downarrow + R—\overset{O}{\overset{\|}{C}}—O^- + 4NH_3 + 2H_2O$$

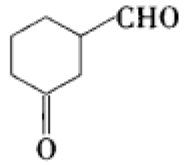
aldehyde Tollens reagent silver carboxylate

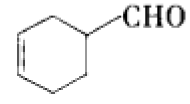
PROBLEM 19–25

Predict the major products of the following reactions.

(a)  $+ Ag_2O$

(b)  $+ K_2Cr_2O_7/H_2SO_4$

(c)  $+ \overset{+}{Ag}(NH_3)_2\ {}^-OH$

(d)  $+ KMnO_4$ (cold, dilute)

19–15 Reductions of Ketones and Aldehydes

19–15A Hydride Reductions (Review)

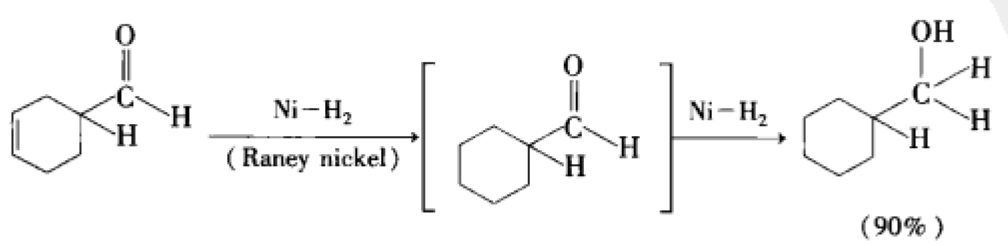
Ketones and aldehydes are most commonly reduced by sodium borohydride. Sodium borohydride ($NaBH_4$) reduces ketones to secondary alcohols and aldehydes to primary alcohols. Lithium aluminum hydride ($LiAlH_4$) also accomplishes these reductions, but it is a more powerful reducing agent, and it is much more difficult to work with. Sodium borohydride is preferred for simple reductions of ketones and aldehydes.

$$\underset{\text{2-butanone}}{CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_3} \xrightarrow{NaBH_4,\ CH_3OH} \underset{(\pm)\text{2-butanol (100\%)}}{CH_3-\overset{OH}{\overset{|}{C}H}-CH_2CH_3}$$

19–15B Catalytic Hydrogenation

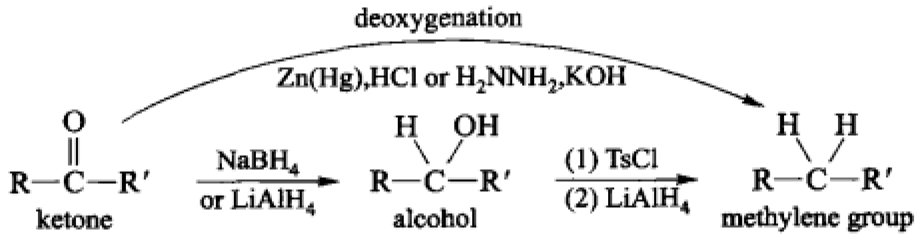
Like alkene double bonds, carbonyl double bonds can be reduced by catalytic hydrogenation. Catalytic hydrogenation is slower with carbonyl groups than with olefinic double bonds, however. Before sodium borohydride was available, catalytic hydrogenation was often used to reduce aldehydes and ketones, but any olefinic double bonds were reduced as well. In the laboratory, we prefer sodium borohydride over catalytic reduction because it reduces ketones and aldehydes faster than olefins, and no gas-handling equipment is required. Catalytic hydrogenation is still widely used in industry, however, because H_2 is much cheaper than $NaBH_4$, and pressure equipment is more readily available there.

The most common catalyst for catalytic hydrogenation of ketones and aldehydes is **Raney nickel.** Raney nickel is a finely divided hydrogen-bearing form of nickel made by treating a nickel-aluminum alloy with a strong sodium hydroxide solution. The aluminum in the alloy reacts to form hydrogen, leaving behind a finely divided nickel powder saturated with hydrogen. Pt and Rh catalysts are also used for hydrogenation of ketones and aldehydes.

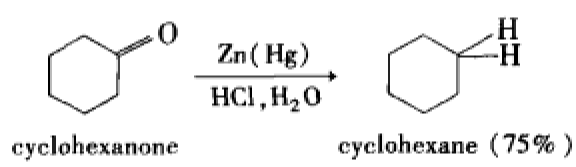


19-15C Deoxygenation of Ketones and Aldehydes

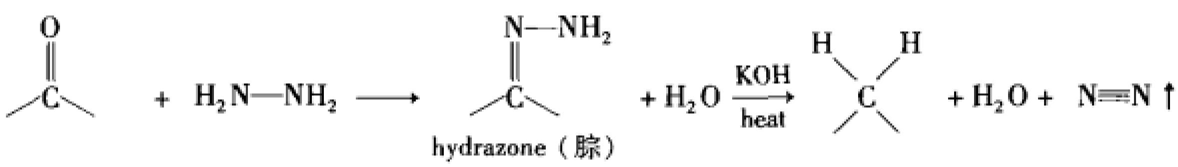
A *deoxygenation* replaces the carbonyl oxygen atom of a ketone or aldehyde with two hydrogen atoms, reducing the carbonyl group past the alcohol stage all the way to a methylene group. The following equation compares deoxygenation with the common hydride reductions that give alcohols.



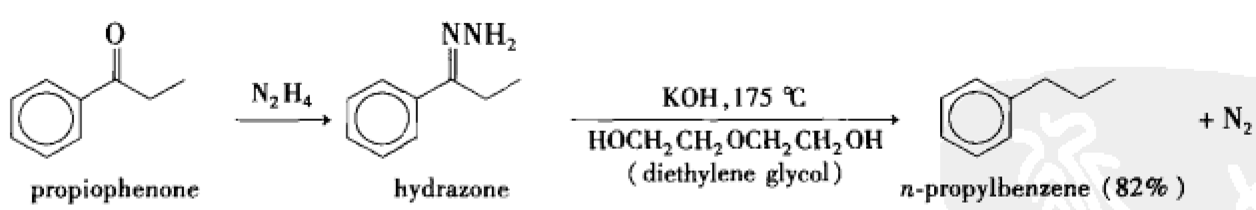
Clemmensen Reduction The **Clemmensen reduction** is most commonly used to convert acylbenzenes from Friedel-Crafts acylation to alkylbenzenes, but it also works with other ketones and aldehydes that are not sensitive to acid. The carbonyl compound is heated with an excess of amalg amated zinc (zinc treated with mercury) and hydrochloric acid. The actual reduction occurs by a complex mechanism on the surface of the zinc.



Wolff-Kishner Reduction Compounds that cannot survive treatment with hot acid can be deoxygenated using the **Wolff-Kishner reduction.** The ketone or aldehyde is converted to its hydrazone, which is heated with a strong base such as KOH or potassium *t*-butoxide. Ethylene glycol, diethylene glycol, or another highboiling solvent is used to facilitate the high temperature (140-200 ℃) needed in the second step.

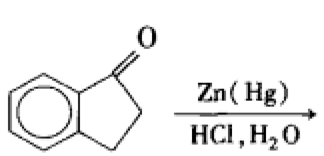


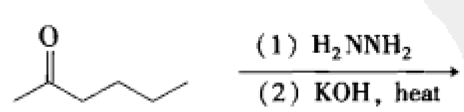
Examples

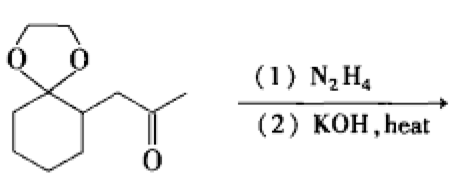


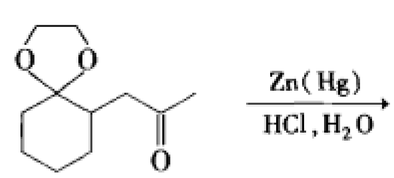
PROBLEM 19-26

Predict the major products of the following reactions:

(a) 

(b) 

(c) 

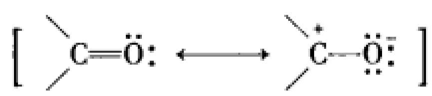
(d) 

Summary in Chinese

本 章 概 要

一、酮、醛的结构

羰基（$\rangle$C=O）是醛、酮的特征官能团。在酮、醛分子中，羰基碳原子以 sp^2 杂化与其他三个原子形成三个 σ 键，羰基碳原子的 p 轨道与氧原子的 p 轨道相互平行侧面重叠形成 π 键。羰基碳原子与基相连的三个原子处于同一平面内，相互间的键角约为 120°，而 π 键是垂直于这个平面的。在羰基中由于氧原子的电负性大于碳原子，使羰基中双键的电子云偏向氧原子，羰基具有极性：



碳原子是缺电子中心，即羰基碳原子有一定的亲电性，而羰基氧原子上带有部分负电荷，有一定的碱性。

二、酮、醛的物理性质

羰基是极性较强的基团，其沸点较相对分子质量相近的烃、卤烃、醚的高；但由于酮（醛）分子之间不能形成氢键，故其沸点较相对分子质量相近的醇、酸的低。低碳数的酮、醛与水能形成氢键，它们在水中有一定的溶解度，其中甲醛、乙醛与水以任意比例互溶。

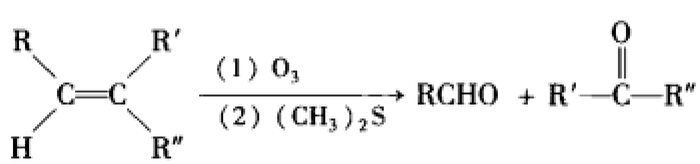
三、醛、酮的制备

1. 醇的氧化（oxidation of alcohols）：

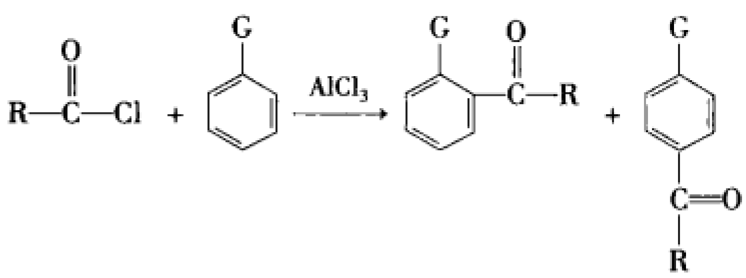
$$R-CH(OH)-R' \xrightarrow{Na_2Cr_2O_7/H_2SO_4} R-\overset{O}{\overset{\|}{C}}-R'$$

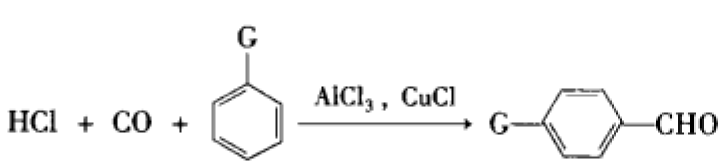
$$R-CH_2OH \xrightarrow{C_5H_5NH^+CrO_3Cl^-\,(PCC)} R-\overset{O}{\overset{\|}{C}}-H$$

2. 烯烃的臭氧化分解（ozonolysis of alkenes）：



3. Friedel-Crafts 酰基化：

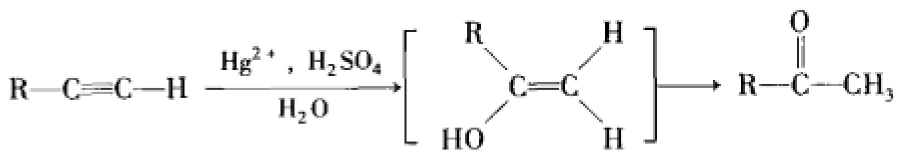




（the Gatterman-Koch formylation）

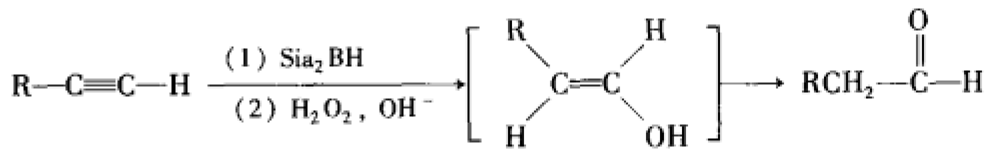
☆ G = H、X、活化基团。

4. 炔烃的水合反应：



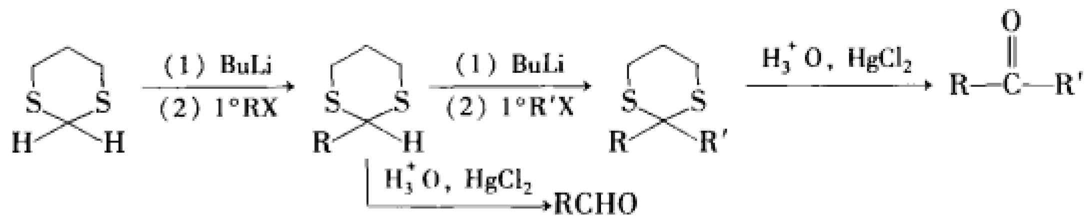
☆ Markovnikov 定向。

5. 炔烃的硼氢化-氧化反应：

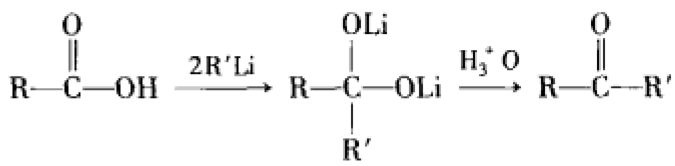


☆ 反 Markovnikov 定向。

6. 1,3－二噻烷的烷基化(alkylation of 1,3-dithianes)：

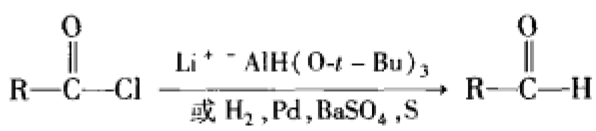


7. 用有机锂试剂与羧酸反应合成酮(synthesis of ketones using organolithium with carboxylic acids)：



8. 从腈合成酮(synthesis of ketones from nitriles)：

9. 酰氯还原合成醛(aldehyde synthesis by reduction of acid chlorides)：



10. 从酰氯合成酮(ketones synthesis from acid chlorides)：

四、醛、酮的化学性质

1. 亲核加成反应(nucleophilic addition)：由于羰基碳原子高度缺电子，容易受亲核试剂进攻而发生亲核加成反应。亲核试剂的中心原子可以是碳原子(如：NaCN、RMgX、RLi、$Ph_3P=CH_2$ 中的碳原子)，也可以是带有未共用电子对的氧、氮、磷等杂原子(如：H_2O、ROH、氨及其衍生物)。

(1) 亲核加成反应机理：强亲核试剂如 RMgX、RLi 等对羰基的亲核加成可顺利地进行，而较弱的亲核试剂如 H_2O、ROH 等与羰基的亲核加成反应往往是可逆的，且需要酸或碱催化。碱催化原理是增加亲核试剂的亲核性，酸催化原理是增加羰基碳原子的亲电性。

● **碱催化：**

$$\text{H—Nuc} + \text{B}^- \rightleftharpoons \text{H—B} + \text{Nuc}^-$$

如 $CH_3OH + OH^- \longrightarrow CH_3O^- + H_2O$

弱亲核试剂 强亲核试剂

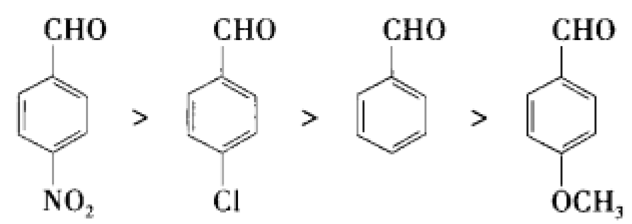
● 酸催化：

$$>C{=}\ddot{O}: + H^+ \rightleftharpoons \left[>C{=}\overset{+}{\ddot{O}}H \longleftrightarrow >\overset{+}{C}{-}\ddot{O}H \right]$$

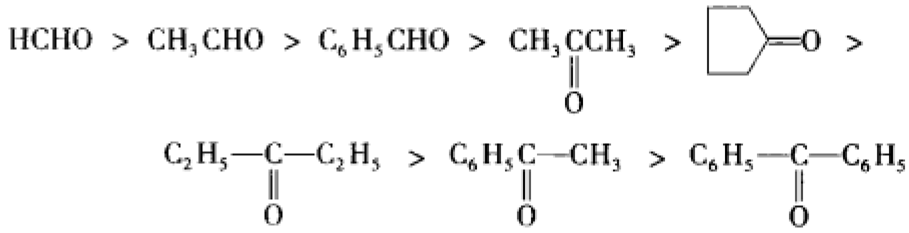
碳原子电正性增加

（2）影响亲核加成反应活性的因素：空阻效应（steric effect）的影响：亲核加成反应活性与羰基相连的烃基的大小及电子效应密切相关。由于羰基是 sp^2 杂化，亲核加成产物是 sp^3 杂化，由 sp^2 杂化转化为 sp^3 杂化时，分子内中心碳原子周围的基团数目增加，基团之间拥挤程度增加。因此，基团体积越大，活化能越高，这种反应越不易进行。同理，亲核试剂的体积越大，反应越不易进行。

电子效应（electronic effect）的影响：羰基碳的缺电子程度越大，越容易受亲核试剂进攻，亲核加成反应活性越高。例如，亲核加成反应活性次序为：



综合电子效应和空间效应，下面化合物亲核加成反应活性次序为：



（3）与氢氰酸的反应：

$$R{-}\overset{O}{\overset{\|}{C}}{-}R'(H) + HCN \xrightleftharpoons{^-CN} R{-}\underset{CN}{\underset{|}{\overset{OH}{\overset{|}{C}}}}{-}R'(H)$$

☆ 产物 α-羟基氰水解可制备 α-羟基酸。

（4）与醇的反应：

$$R{-}\overset{O}{\overset{\|}{C}}{-}R'(H) + 2\,R''OH \xrightleftharpoons{H^+} R{-}\underset{OR''}{\underset{|}{\overset{OR''}{\overset{|}{C}}}}{-}R'(H)$$

缩酮（醛）

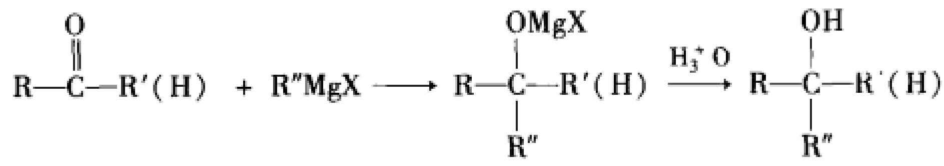
☆ 缩酮（醛）在中性或碱性条件下较稳定，酸性水解可生成原来的酮（醛）；在有机合成上，该反应用于酮（醛）羰基的保护。

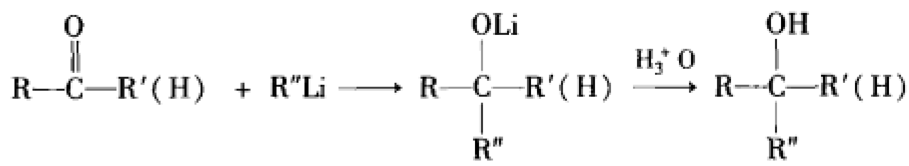
（5）与氨及其衍生物的反应：

$$R{-}\overset{O}{\overset{\|}{C}}{-}R'(H) + H_2N{-}Z \xrightarrow{H^+} R{-}\overset{N{-}Z}{\overset{\|}{C}}{-}R'(H) \quad (Z = {-}OH, {-}NH_2, {-}NH\overset{O}{\overset{\|}{C}}NH_2, {-}NHPh, {-}H, {-}R)$$

☆ 可逆平衡反应；亲核加成－消除机理；用于鉴定、提纯酮（醛）；制备含氮化合物，将“C═O”转化为“C═N”。

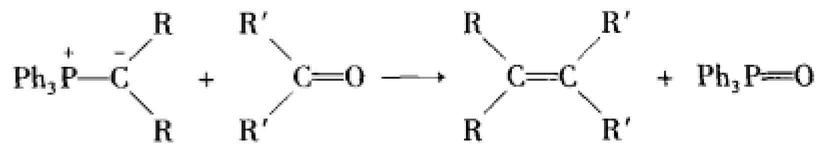
(6) 与金属有机化合物(RMgX、RLi)的反应:





☆ 该反应可用于制备伯、仲、叔醇;活性 RLi > RMgX。

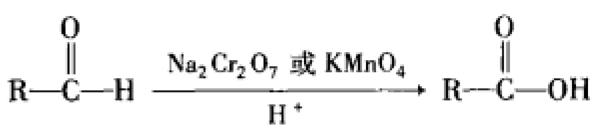
(7) 与磷叶立德的反应——Wittig 反应:



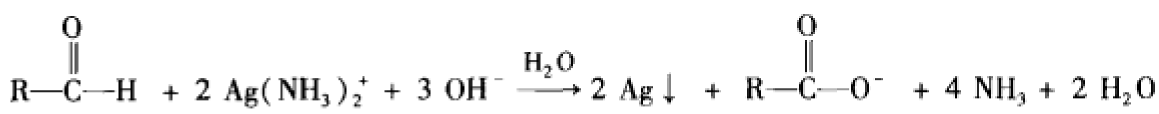
☆ 用于将"C=O"转化为"C=C"的合成反应。

2. 醛的氧化(oxidation of aldehydes):

(1) 被 $Na_2Cr_2O_7$ 或 $KMnO_4$ 氧化:



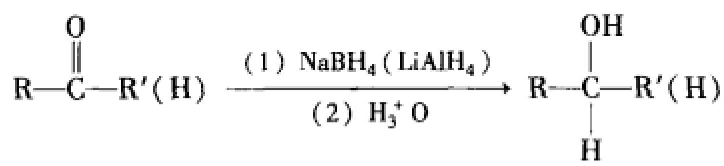
(2) Tollens 试验:



☆ 此反应用于鉴别醛。

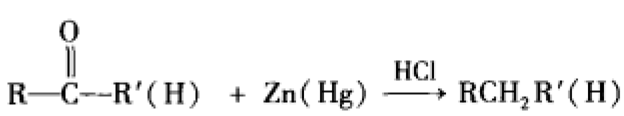
3. 羰基还原反应(reduction reactions carbonyl group):

(1) 被 $NaBH_4$ 或 $LiAlH_4$ 还原:



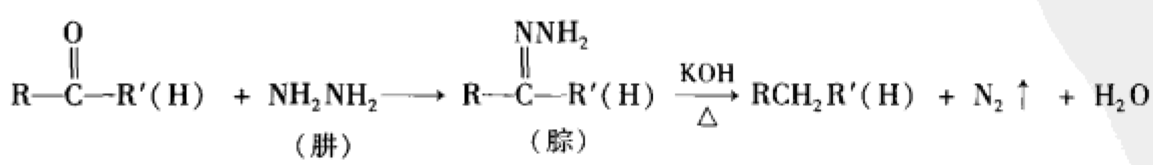
☆ 醛、酮转化成醇,活性 $LiAlH_4 > NaBH_4$。

(2) Clemmensen 还原:



☆ 酸性条件下,将"C=O"还原为"CH_2";不适合对酸敏感的体系。

(3) Wolff-Kishner 还原:



☆ 碱性条件下,将"C=O"还原为"CH_2";不适合对碱敏感的体系。

Essential Problem-Solving Skills in Chapter 19

1. Use spectral information to determine the structures.
2. Write equations for syntheses of ketones and aldehydes from alcohols, alkenes, alkynes, carboxylic acids, nitriles, acid chlorides, dithianes, and aromatic compounds.
3. Propose effective single-step and multistep syntheses of ketones and aldehydes.
4. Predict the products of reactions of ketones and aldehydes with the following types of compounds (give mechanisms where appropriate):
   (a) hydride reducing agents; Clemmensen and Wolff–Kishner reagents
   (b) Grignard and organolithium reagents
   (c) phosphorus ylides
   (d) water
   (e) hydrogen cyanide
   (f) ammonia and primary amines
   (g) hydroxylamine and hydrazine derivatives
   (h) alcohols
   (i) oxidizing agents
5. Use your knowledge of the mechanisms of ketone and aldehyde reactions to propose mechanisms and products of similar reactions you have never seen before.
6. Show how to convert ketones and aldehydes to other functional groups.
7. Use retrosynthetic analysis to propose effective multistep syntheses using ketones and aldehydes as intermediates and protecting the carbonyl group if necessary.

Study Problems

19–27 Define each term and give an example.

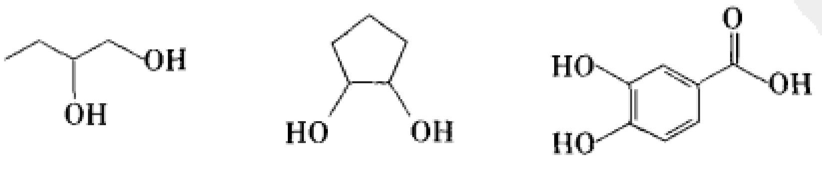
(a) ketone (b) aldehyde (c) enol form (d) cyanohydrin
(e) imine (f) hydrate (g) carbinolamine (h) oxime
(i) phenylhydrazone (j) 2,4-DNP derivative (k) semicarbazone (l) acetal
(m) Wittig reaction (n) ethylene acetal (o) hemiacetal (p) Tollens test
(q) Wolff-Kishner reduction (r) Clemmensen reduction (s) ketal

19–28 Rank the following carbonyl compounds in order of increasing equilibrium constant for hydration:

CH_3COCH_2Cl $ClCH_2CHO$ CH_2O CH_3COCH_3 CH_3CHO

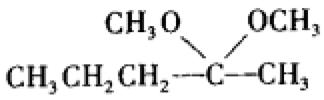
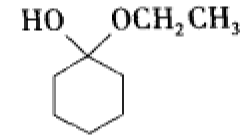
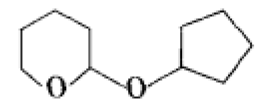
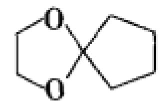
19–29 A compound of formula $C_6H_{10}O_2$ shows only two absorptions in the proton NMR: a singlet at 2.67 and a singlet at 2.15. These absorptions have areas in the ratio 2 : 3. The IR spectrum shows a strong absorption at 1708 cm^{-1}. Propose a structure for this compound.

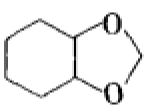
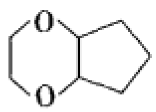
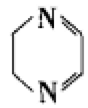
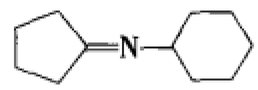
19–30 Acetals can serve as protecting groups for 1,2-diols, as well as for aldehydes and ketones. When the acetal is formed from acetone plus the diol, the acetal is called an acetonide. Show the acetonides formed from these diols with acetone under acid catalysis.



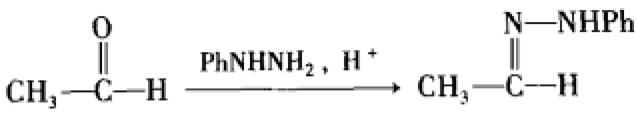
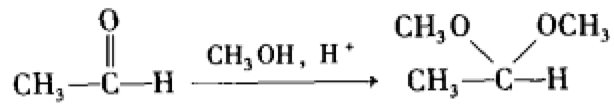
19–31 For each compound,

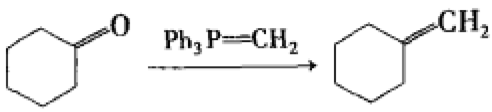
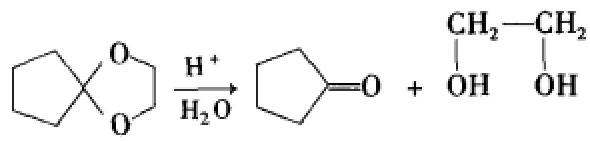
1. Name the functional group.
2. Show what compound(s) result from complete hydrolysis.

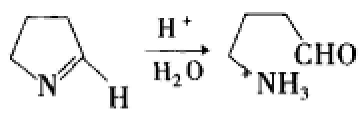
(a) 
(b) 
(c) 
(d) 

(e) 
(f) 
(g) 
(h) 

19−32 Propose mechanisms for the following reactions.

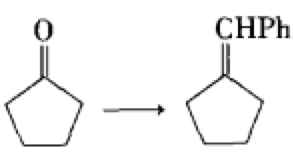
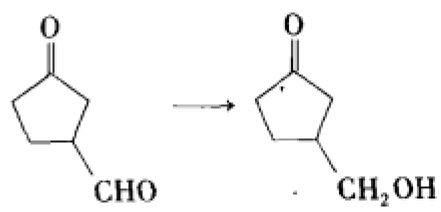
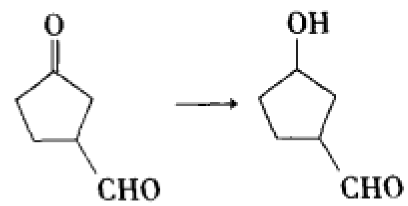
(a) 
(b) 

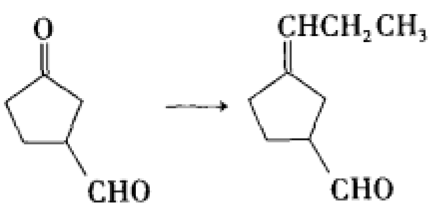
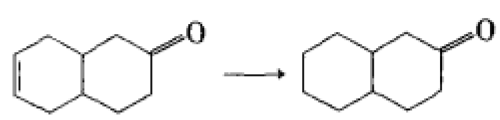
(c) 
(d) 

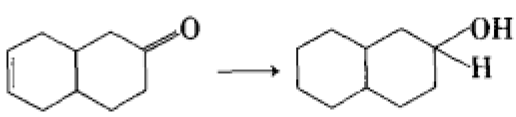
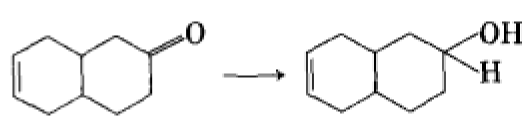
(e) 

19−33 Show how you would accomplish the following syntheses efficiently and in good yield. You may use any necessary reagents.

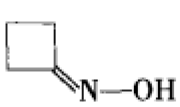
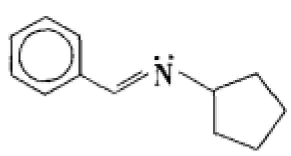
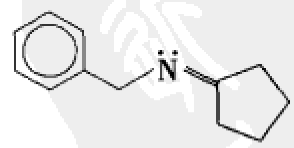
(a) acetaldehyde ⟶ lactic acid, $CH_3CH(OH)COOH$

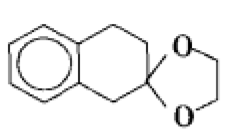
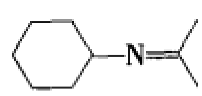
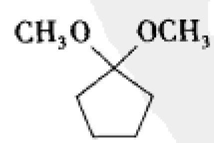
(b) 
(c) 
(d) 

(e) 
(f) 

(g) 
(h) 

19−34 Show how you would synthesize the following derivatives from appropriate carbonyl compounds.

(a) 
(b) 
(c) 

(d) 
(e) 
(f) 

19−35 Draw structures of the following derivatives.

(a) the 2, 4-dinitrophenylhydrazone of benzaldehyde
(b) the semicarbazone of cyclobutanone
(c) cyclopropanone oxime
(d) the ethylene ketal of 3-hexanone
(e) acetaldehyde dimethyl acetal
(f) the methyl hemiacetal of formaldehyde
(g) the (*E*) isomer of the ethyl imine of propiophenone
(h) the dithiane thioacetal of propanal

19−36 Predict the products formed when cyclohexanone reacts with the following reagents.

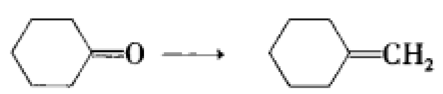
(a) CH_3NH_2, H^+
(b) excess CH_3OH, H^+
(c) hydroxylamine and weak acid
(d) ethylene glycol and *p*-toluenesulfonic acid
(e) phenylhydrazine and weak acid
(f) PhMgBr and then mild H_3O^+
(g) Tollens reagent
(h) sodium acetylide, then mild H_3O^+
(i) hydrazine, then hot, fused KOH
(j) $Ph_3P{=}CH_2$
(k) sodium cyanide
(l) acidic hydrolysis of the product from (k)

19−37 Both $NaBH_4$ and $NaBD_4$ are commercially available, and D_2O is common and inexpensive. Show how you would synthesize the following labeled compounds, starting with 2-butanone.

(a) $CH_3{-}C(OH)(D){-}CH_2{-}CH_3$ (b) $CH_3{-}C(OD)(D){-}CH_2{-}CH_3$ (c) $CH_3{-}C(OD)(H){-}CH_2{-}CH_3$

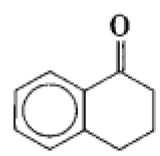
19−38 When $LiAlH_4$ reduces 3-methylcyclopentanone, the product mixture contains 60% *cis*-3-methylcyclopentanol and 40% *trans*-3-methylcyclopentanol. Use your models and make three-dimensional drawings to explain this prefe-rence for the cis isomer.

19−39 The Wittig reaction is useful for placing double bonds in less stable positions. For example, the following transformation is easily accomplished using a Wittig reaction.



cyclohexanone methylenecyclohexane

(a) Show how you would use a Wittig reaction to do this.
(b) Show how you might do this *without* using a Wittig reaction, and explain why the Wittig reaction is a much better synthesis.

19−40 Show how you would accomplish the following syntheses.
(a) benzene ⟶ *n*-butylbenzene
(b) benzonitrile ⟶ propiophenone
(c) benzene ⟶ *p*-methoxybenzaldehyde
(d) Ph—$(CH_2)_4$—OH ⟶ 

tetralone

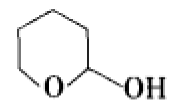
19−41 Predict the products formed when cyclohexanecarbaldehyde reacts with the following reagents.
(a) PhMgBr, then H_3O^+
(b) Tollens reagent
(c) semicarbazide and weak acid
(d) excess ethanol and acid
(e) 1, 3-propanedithiol, H^+
(f) zinc amalgam and dilute hydrochloric acid

19−42 Show how you would synthesize 2-octanone from each compound. You may use any necessary reagents.
(a) heptanal
(b) 1-octyne
(c) 1, 3-dithiane
(d) 2-octanol
(e) heptanoic acid
(f) $CH_3(CH_2)_5CN$
(g) 2, 3-dimethyl-2-nonene

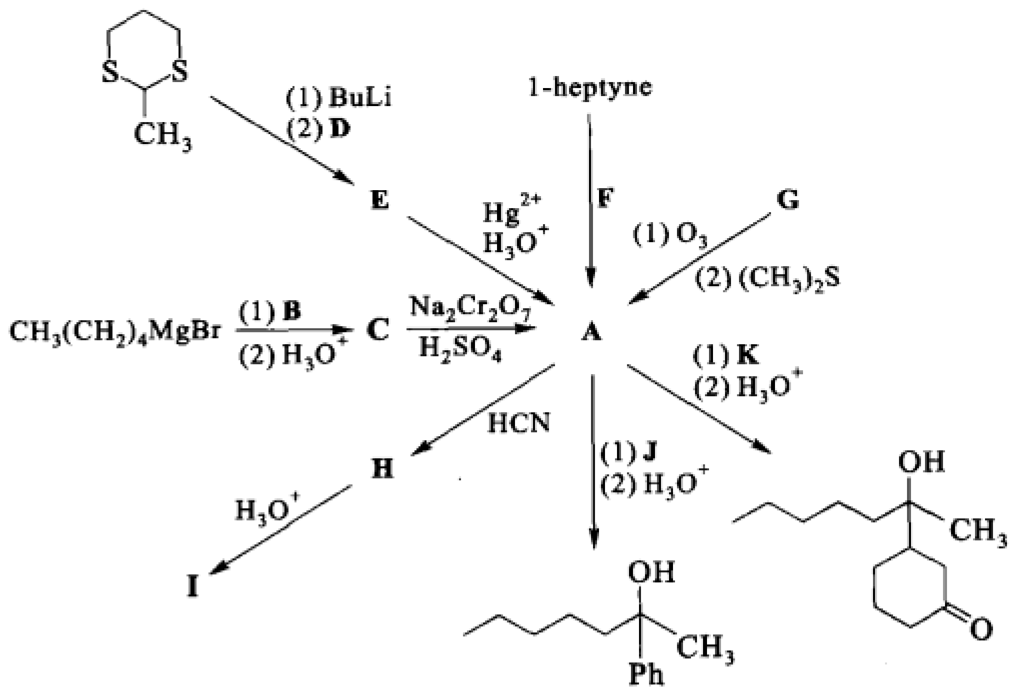
19−43 Show how you would synthesize octanal from each compound. You may use any necessary reagents.
(a) 1-octanol
(b) 1-nonene
(c) 1-octyne
(d) 1, 3-dithiane
(e) 1, 1-dichlorooctane
(f) octanoic acid

19−44 Hydration of alkynes (via oxymercuration) gives good yields of single compounds only with symmetrical or terminal alkynes. Show what the products would be from hydration of each compound.
(a) 3-hexyne
(b) 2-hexyne
(c) 1-hexyne
(d) cyclodecyne
(e) 3-methylcyclodecyne

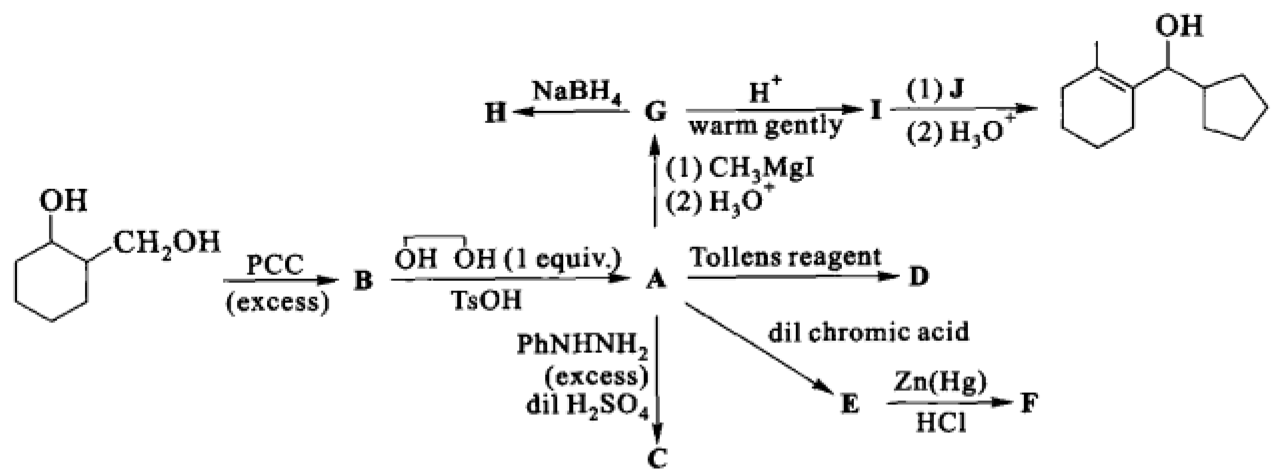
19−45 Which of the following compounds would give a positive Tollens test? (Remember that the Tollens test involves mild basic aqueous conditions.)
(a) $CH_3CH_2CH_2COCH_3$
(b) $CH_3CH_2CH_2CH_2CHO$
(c) $CH_3CH{=}CH{-}CH{=}CH{-}OH$

(d) $CH_3CH_2CH_2CH_2—CH(OH)OCH_3$ (e) $CH_3CH_2CH_2CH_2—CH(OCH_3)_2$ (f) 

19-46 Solving the following road-map problem depends on determining the structure of **A**, the key intermediate. Give structures for compounds **A** through **K**.

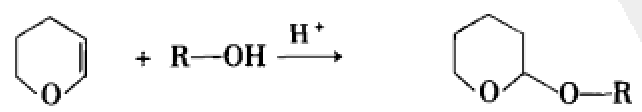


19-47 The following road-map problem centers on the structure and properties, of **A**, a key intermediate in these reactions. Give structures for compounds **A** through **J**.



·19-48 A dithiane synthesis can convert an aldehyde to a ketone. The aldehyde is first converted to its dithiane derivative, which is deprotonated and alkylated. A mercuric chloride-assisted hydrolysis gives the ketone. Show how this technique might be used to convert benzaldehyde to benzyl phenyl ketone.

·19-49 Under acid catalysis, an alcohol reacts with dihydropyran to give the tetrahydropyranyl derivative (called a "THP ether") of the alcohol.



dihydropyran

tetrahydropyranyl derivative
R—O—THP, a "THP ether"

(a) Propose a mechanism for this reaction.

(b) The "THP ether" is not an ether. What functional group does it actually contain? How will it react under basic conditions? Under acidic conditions?

(c) Propose a mechanism for hydrolysis of the THP derivative in dilute aqueous acid, and predict the products.

Chapter 20

Amines

20−1 Introduction

Amines are organic derivatives of ammonia with one or more alkyl or aryl groups bonded to the nitrogen atom. As a class, amines include some of the most important biological compounds. Amines serve many functions in living organisms, such as bioregulation, neurotransmission, and defense against predators. Because of their high degree of biological activity, many amines are used as drugs and medicines. The structures and uses of some important biologically active amines are shown in Figure 20−1.

The *alkaloids* are an important group of biologically active amines, mostly synthesized by plants to protect them from being eaten by insects and other animals. The structures of some representative alkaloids are shown in Figure 20−2. Although some alkaloids are used medicinally (chiefly as painkillers), all alkaloids are toxic and cause death if taken in large quantities. The Greeks chose the alkaloid coniine to kill Socrates, although morphine, nicotine, or cocaine would have served equally well.

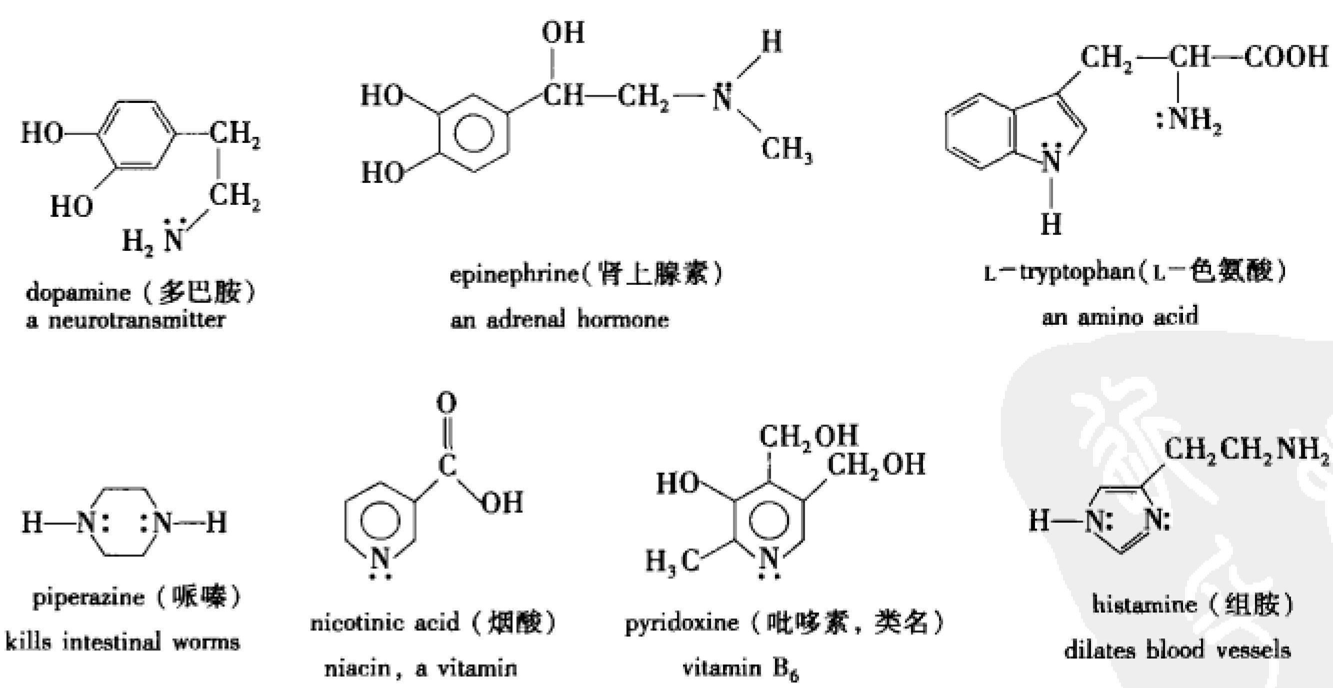
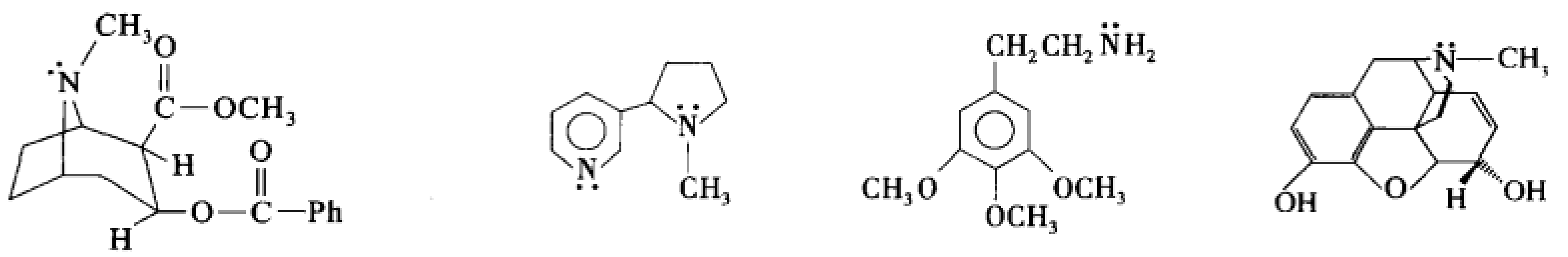


Figure 20−1 Examples of some biologically active amines.

Mild cases of alkaloid poisoning can produce psychological effects that resemble peacefulness, euphoria, or hallucinations. People seeking these effects often become addicted to alkaloids. Alkaloid addiction often ends in death; current estimates are over 400 000 deaths in the United States per year, including both natural alkaloids like nicotine and cocaine, and synthetic alkaloids like amphetamine.

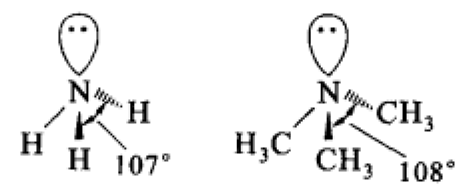


cocaine (可卡因) in coca leaves | nicotine(尼古丁;烟碱) in tobacco | mescaline (墨斯卡灵) in peyote cactus | morphine (吗啡) in opium poppies

Figure 20-2 Some representative alkaloids.

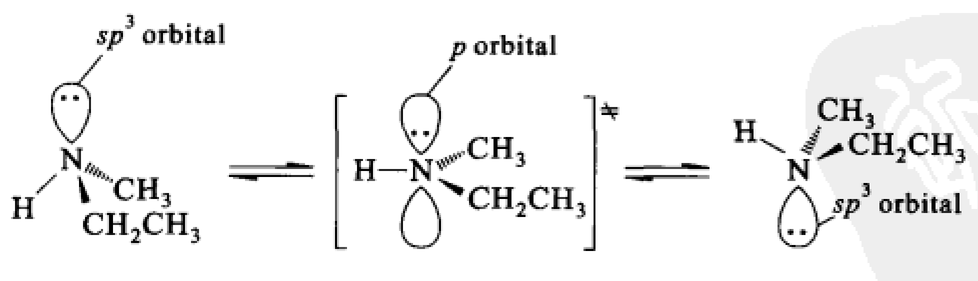
20-2 Structure of Amines

Ammonia has a slightly distorted tetrahedral shape. A lone pair of nonbonding electrons occupies one of the tetrahedral positions. This geometry is represented by sp^3 hybridization of nitrogen, with the bulky lone pair compressing the H—N—H bond angles to 107° from the "ideal" sp^3 bond angle of 109.5°. Trimethylamine shows less angle compression because the bulky methyl groups open the angle slightly.



ammonia trimethylamine

A tetrahedral amine with three different substituents (and a lone pair) is nonsuperimposable on its mirror image. In most cases, we cannot resolve such an amine into two enantiomers, however, because the enantiomers interconvert rapidly (see Figure 20-3). This interconversion takes place by **nitrogen inversion**, in which the lone pair moves from one face of the molecule to the other. The nitrogen atom is sp^2 hybridized in the transition state, and the nonbonding electrons occupy a p orbital. This is a fairly stable transition state, as reflected by the small activation energy of about 25 kJ/mol. Interconversion of (R)-and (S)-ethylmethylamine is shown in Figure 20-3. In naming the enantiomers of chiral amines, the Cahn-Ingold-Prelog convention is used, with the nonbonding electron pair having the lowest priority.



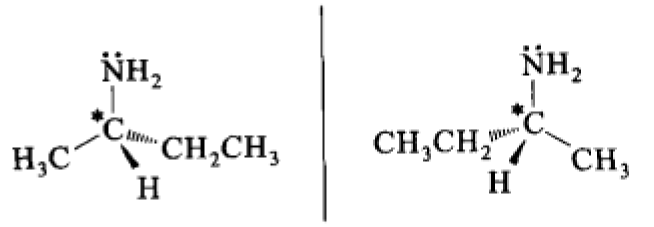
(R)-ethylmethylamine [transition state] (S)-ethylmethylamine

Figure 20-3 Nitrogen inversion interconverts the two enantiomers of a simple chiral amine. The transition state is a planar, sp^2-hybrid structure with the lone pair in a p orbital.

Although most simple amines cannot be resolved into enantiomers, several types of chiral amines can be resolved:

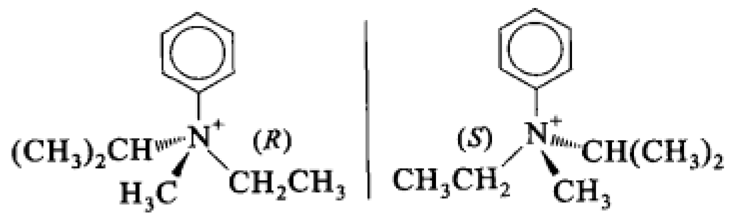
1. *Amines whose chirality stems from the presence of asymmetic carbon atoms.* For example, 2-butanamine

can be resolved into enantiomers because the 2-butyl group is chiral.

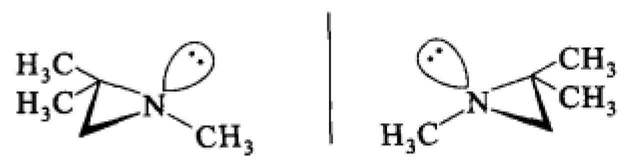


(*S*)-2-butanamine (*R*)-2-butanamine

2. *Quaternary ammonium salts with asymmetic nitrogen atoms.* Inversion of configuration is not possible because there is no lone pair to undergo nitrogen inversion. For example, the methyl ethyl isopropyl anilinium salts can be resolved into enantiomers.



3. *Amines that cannot attain the sp^2-hybrid transition state for nitrogen inversion.* If the nitrogen atom is contained in a small ring, for example, it is prevented from attaining the 120° bond angles that facilitate inversion. Such a compound has a higher activation energy for inversion, the inversion is slow, and the enantiomers may be resolved. Chiral aziridines (three-membered rings containing a nitrogen) often may be resolved into enantiomers.



(*R*)-1,2,2-trimethylaziridine
[(*R*)-1,2,2-三甲基氮杂环丙烷]

(*S*)-1,2,2-trimethylaziridine

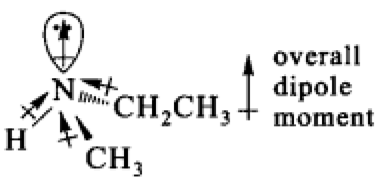
PROBLEM 20-1

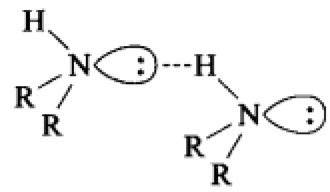
Which of the amines listed next can be resolved into enantiomers? In each case, explain why interconversion of the enantiomers would or would not take place.

(a) *cis*-2-methylcyclohexanamine
(b) *N*-methyl-*N*-ethylcyclohexanamine
(c) *N*-methylaziridine
(d) ethylmethylanilinium iodide
(e) methylethylpropylisopropylammonium iodide

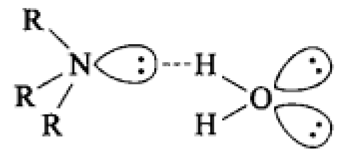
20-3 Physical Properties of Amines

Amines are strongly polar because the large dipole moment of the lone pair of electrons adds to the dipole moments of the C ↔ H and H ↔ N bonds. Primary and secondary amines have N—H bonds, allowing them to form hydrogen bonds. Having no N—H bonds, pure tertiary amines cannot engage in hydrogen bonding. They can, however, accept hydrogen bonds from molecules having O—H or N—H bonds.





1° or 2° amine:
hydrogen bond donor and acceptor



3° amine:
hydrogen bond acceptor only

Because nitrogen is less electronegative than oxygen, the N—H bond is less polar than the O—H bond. Therefore, amines form weaker hydrogen bonds than do alcohols of similar molecular weights. Primary and secondary amines have boiling points that are lower than those of alcohols, yet higher than those of ethers of similar molecular weights, With no hydrogen bonding, tertiary amines have lower boiling points than primary and secondary amines of similar molecular weights. Table 20-1 compares the boiling points of an ether, an alcohol, and amines of similar molecular weights.

TABLE 20-1 Comparison of the Boiling Points of an Ether, an Alcohol, and Amines of Similar Molecular Weights

Compound	bp/℃	Type	Molecular Weight
$(CH_3)_3N$:	3	tertiary amine	59
CH_3—O—CH_2—CH_3	8	ether	60
CH_3—NH—CH_2—CH_3	37	secondary amine	59
$CH_3CH_2CH_2$—NH_2	48	primary amine	59
$CH_3CH_2CH_2$—OH	97	alcohol	60

All amines, even tertiary ones, form hydrogen bonds with hydroxylic solvents such as water and alcohols. Therefore, amines tend to be soluble in alcohols, and the lower-molecular-weight amines (up to about six carbon atoms) are relatively soluble in water. Table 20-2 lists the melting points, boiling points, and water solubilities of some simple aliphatic and aromatic amines.

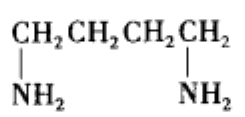
TABLE 20-2 Melting Points, Boiling Points, and Water Solubilities of Some Simple Amines

Structure	Molecular Weight	mp/℃	bp/℃	H_2O Solubility
		Primary amines		
CH_3NH_2	31	-93	-7	very soluble
$CH_3CH_2NH_2$	45	-81	17	∞
$CH_3CH_2CH_2NH_2$	59	-83	48	∞
$(CH_3)_2CHNH_2$	59	-101	33	∞
$CH_3CH_2CH_2CH_2NH_2$	73	-50	77	∞
$(CH_3)_2CHCH_2NH_2$	73	-86	68	∞
$CH_3CH_2CH(NH_2)CH_3$	73	-104	63	∞
$(CH_3)_3CNH_2$	73	-68	45	∞
cyclo-$C_6H_{11}NH_2$	99		134	slightly soluble
$C_6H_5CH_2NH_2$	107		185	∞
CH_2=CH—CH_2NH_2	57		53	very soluble

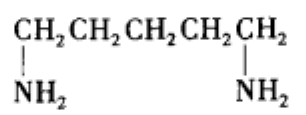
Continue

Structure	Molecular Weight	mp/ ℃	bp/ ℃	H_2O Solubility
$C_6H_5NH_2$	93	-6	184	3.7%
		Secondary amines		
$(CH_3)_2NH$	45	-96	7	very soluble
$CH_3CH_2NHCH_3$	59		37	very soluble
$(CH_3CH_2)_2NH$	73	-42	56	very soluble
$(CH_3CH_2CH_2)_2NH$	101	-40	111	slightly soluble
$[(CH_3)_2CH]_2NH$	101	-61	84	slightly soluble
$(CH_3CH_2CH_2CH_2)_2NH$	129	-59	159	slightly soluble
$C_6H_5NHCH_3$	107	-57	196	slightly soluble
$(C_6H_5)_2NH$	169	54	302	insoluble
		Tertiary amines		
$(CH_3)_3N$	59	-117	3.5	very soluble
$(CH_3CH_2)_3N$	101	-115	90	14%
$(CH_3CH_2CH_2)_3N$	143	-94	156	slightly soluble
$C_6H_5N(CH_3)_2$	121	2	194	1.4%
$(C_6H_5)_3N$	251	126	225	insoluble

Perhaps the most obvious property of amines is their characteristic odor of rotting fish. Some of the diamines are particularly pungent; the following diamines have common names that describe their odors:



putrescine [腐胺(俗)]
(1,4-butanediamine)



cadaverine [尸胺(俗)]
(1,5-pentanediamine)

PROBLEM 20-2

Rank each set of compounds in order of increasing boiling points.

(**a**) triethylamine, di-*n*-propylamine, *n*-propyl ether

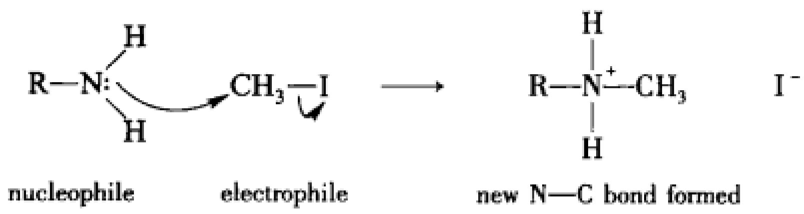
(**b**) ethanol, dimethylamine, dimethyl ether

(**c**) trimethylamine, diethylamine, diisopropylamine

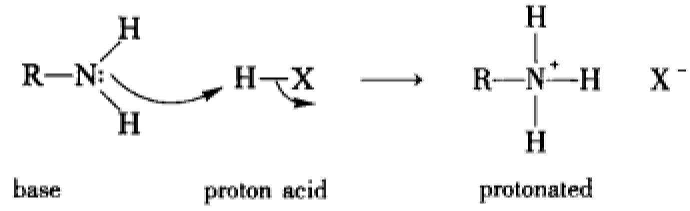
20-4 Basicity of Amines

An amine is a nucleophile (a Lewis base) because its lone pair of nonbonding electrons can form a bond with an electrophile. An amine can also act as a Brønsted-Lowry base by accepting a proton from a proton acid.

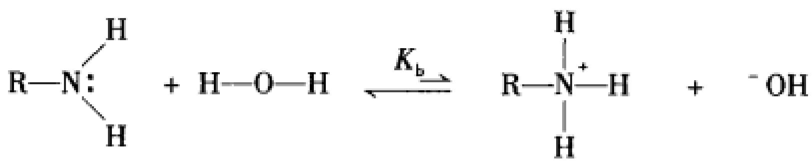
Reaction of an amine as a nucleophile



Reaction of an amine as a proton base



Because amines are fairly strong bases, their aqueous solutions are basic. An amine can abstract a proton from water, giving an ammonium ion and a hydroxide ion. The equilibrium constant for this reaction is called the **base-dissociation constant** for the amine, symbolized by K_b.



$$K_b = \frac{[RNH_3^+][^-OH]}{[RNH_2]} \qquad pK_b = -\lg K_b$$

Values of K_b for most amines are fairly small (about 10^{-3} or smaller), and the equilibrium for this dissociation lies toward the left. Nevertheless, aqueous solutions of amines are distinctly basic, and they turn litmus paper blue.

Because they vary by many orders of magnitude, base-dissociation constants are usually listed as their negative logarithms, or pK_b values. For example, if a certain amine has $K_b = 10^{-3}$, then $pK_b = 3$. Just as we used pK_a values to indicate acid strengths (stronger acids have smaller pK_a values), we use pK_b values to compare the relative strengths of amines as proton bases.

Stronger bases have smaller values of pK_b.

The values of pK_b for some representative amines are listed in Table 20−3.

Some references do not list values of K_b or pK_b for amines. Instead, they list values of K_a or pK_a for the conjugate acid, which is the ammonium ion. We can show that the product of K_a for the ammonium ion and K_b for the amine is K_W, the ion product for water, which is 10^{-14} at room temperature. This is true for any conjugate acid-base pair.

$$\underset{\text{ammonium ion}}{R{-}\overset{+}{N}H_3} + H_2O \xrightarrow{K_a} \underset{\text{amine}}{R{-}\ddot{N}H_2} + H_3O^+$$

$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]} \qquad K_b = \frac{[RNH_3^+][^-OH]}{[RNH_2]}$$

$$K_a \times K_b = [H_3O^+][^-OH] = K_W = 1.0 \times 10^{-14}$$

$$pK_a + pK_b = 14 \qquad pK_b = 14 - pK_a$$

TABLE 20-3 Values of pK_b for Some Representative Amines

Amine	K_b	pK_b	pK_a of R_3N^+H
ammonia	1.8×10^{-5}	4.74	9.26
	Primary alkyl amines		
methylamine	4.3×10^{-4}	3.36	10.64
ethylamine	4.4×10^{-4}	3.36	10.64
n-propylamine	4.7×10^{-4}	3.32	10.68
isopropylamine	4.0×10^{-4}	3.40	10.60
n-butylamine	4.8×10^{-4}	3.32	10.68
cyclohexylamine	4.7×10^{-4}	3.33	10.67
benzylamine	2.0×10^{-5}	4.67	9.33
	Secondary amines		
dimethylamine	5.3×10^{-4}	3.28	10.72
diethylamine	9.8×10^{-4}	3.01	10.99
di-*n*-propylamine	10.0×10^{-4}	3.00	11.00
	Tertiary amines		
trimethylamine	5.5×10^{-5}	4.26	9.74
triethylamine	5.7×10^{-4}	3.24	10.76
tri-*n*-propylamine	4.5×10^{-4}	3.35	10.65
	Aryl amines		
aniline(苯胺)	4.0×10^{-10}	9.40	4.60
N-methylaniline	6.1×10^{-10}	9.21	4.79
N,*N*-dimethylaniline	11.6×10^{-10}	8.94	5.06
p-toluidine(对甲苯胺)	1.2×10^{-9}	8.92	5.08
p-fluoroaniline	4.4×10^{-10}	9.36	4.64
p-chloroaniline	1×10^{-10}	10.0	4.0
p-bromoaniline	7×10^{-11}	10.2	3.8
p-iodoaniline	6×10^{-11}	10.2	3.8
p-methoxyaniline	2×10^{-9}	8.7	5.3
p-nitroaniline	1×10^{-13}	13.0	1.0
	Heterocyclic amines		
pyrrole (吡咯)	1×10^{-15}	≈15	≈ −1
pyrrolidine (四氢吡咯)	1.9×10^{-3}	2.73	11.27
imidazole(咪唑)	8.9×10^{-8}	7.05	6.95
pyridine(吡啶)	1.8×10^{-9}	8.75	5.25
piperidine(哌啶)	1.3×10^{-3}	2.88	11.12

These relationships allow us to convert values of K_a (or pK_a) for the ammonium ion and K_b (or pK_b) for the amine. They also remind us that a strongly basic amine has a weakly acidic ammonium ion and a weakly basic amine has a strongly acidic ammonium ion.

20-5 Effects on Amine Basicity

Figure 20-4 shows an energy diagram for the reaction of an amine with water. On the left are the reactants: the free amine and water. On the right are the products: the ammonium ion and hydroxide ion.

Any structural feature that stabilizes the ammonium ion (relative to the free amine) shifts the reaction toward the right, making the amine a stronger base. Any feature that stabilizes the free amine (relative to the ammonium

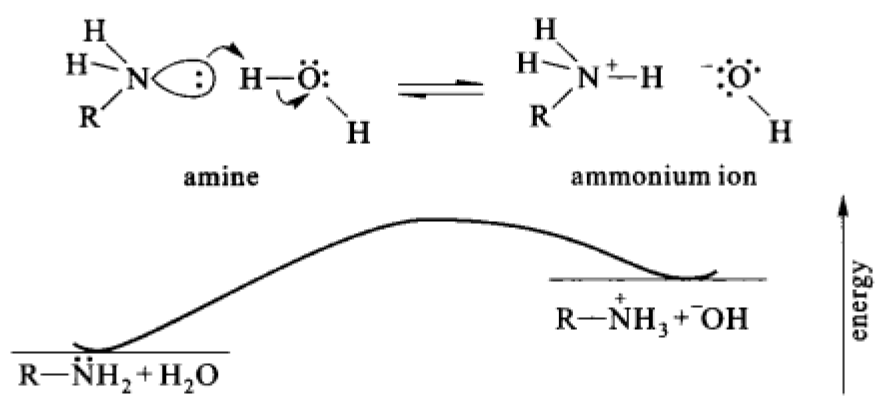
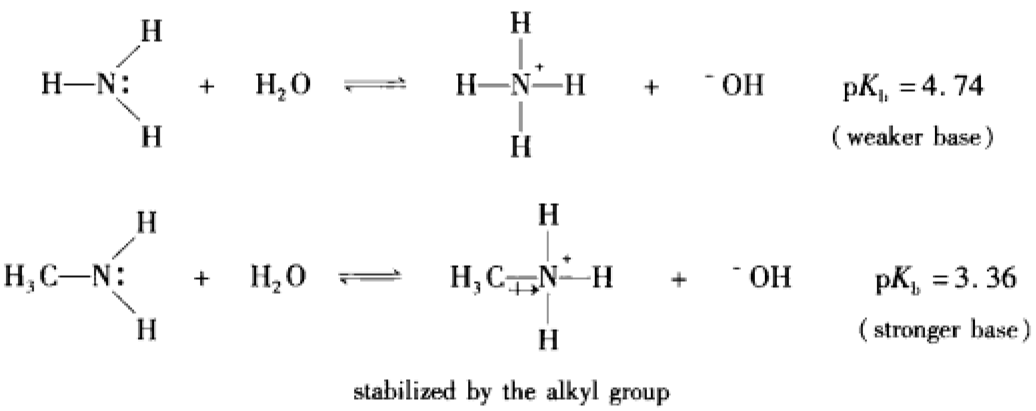


Figure 20-4 Potential-energy diagram of the base-dissociation reaction of an amine.

ion) shifts the reaction toward the left, making the amine a weaker base.

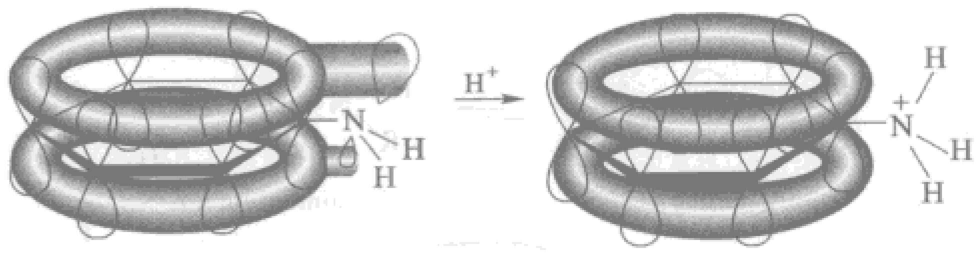
Substitution by Alkyl Groups As an example, consider the relative basicities of ammonia and methylamine. Alkyl groups are electron-donating toward cations, and methylamine has a methyl group to help stabilize the positive charge on nitrogen. This stabilization lowers the potential energy of the methylammonium cation, making methylamine a stronger base than ammonia. The simple alkylamines are generally stronger bases than ammonia.



We might expect secondary amines to be stronger bases than primary amines, and tertiary amines to be the strongest bases of all. The actual situation is more complicated because of solvation effects. Because ammonium ions are charged, they are strongly solvated by water, and the energy of solvation contributes to their stability. The additional alkyl groups around the ammonium ions of secondary and tertiary amines decrease the number of water molecules that can approach closely and solvate the ions. The opposing trends of inductive stabilization and steric hindrance of solvation tend to cancel out in most cases; as a result, primary, secondary, and tertiary amines show similar ranges of basicity.

Resonance Effects on Basicity Aromatic amines (anilines and their derivatives) are weaker bases than simple aliphatic amines (Table 20-3). This reduced basicity is due to resonance delocalization of the nonbonding electrons in the free amine. Figure 20-5 shows how stabilization of the reactant (the free amine) makes the amine less basic. In aniline, overlap between the aromatic ring and the orbital containing nitrogen's lone pair stabilizes the lone pair and makes it less reactive. This overlap is lost in the anilinium ion, so the reactant (aniline) is stabilized compared with the product. The reaction is shifted toward the left, and aniline is less basic than most aliphatic amines.

Resonance effects also influence the basicity of pyrrole. Pyrrole is a very weak base, with a pK_b of about 15. Pyrrole is aromatic because the nonbonding electrons on nitrogen are located in a *p* orbital, where they contribute to the aromatic sextet. When the pyrrole nitrogen is protonated, pyrrole loses its aromatic stabilization. Therefore, protonation on nitrogen is unfavorable, and pyrrole is a very weak base.



aniline(苯胺)
stabilized by overlap with the ring

anilinium ion(苯铵鎓离子)
no overlap is possible

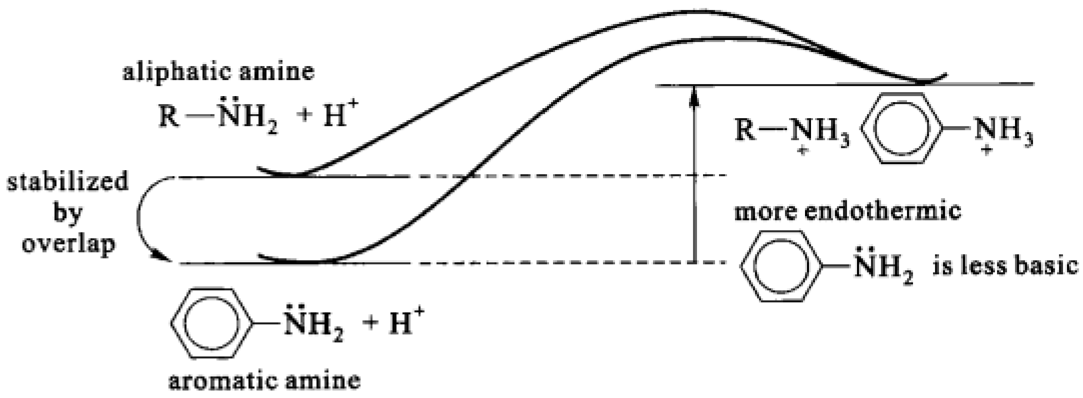
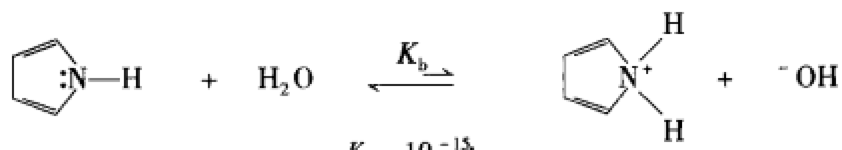


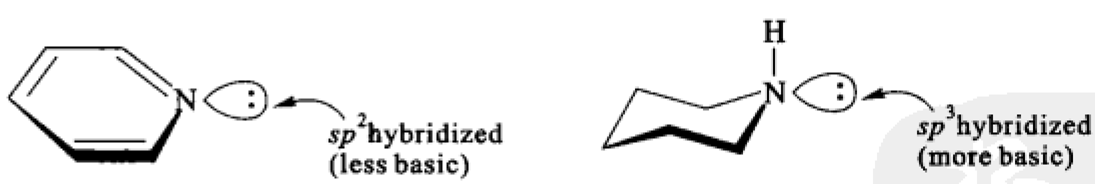
Figure 20-5 Aniline is stabilized by overlap of the lone pair with the aromatic ring. No such overlap is possible in the anilinium ion.



pyrrole(吡咯)
(aromatic)

protonated
(not aromatic)

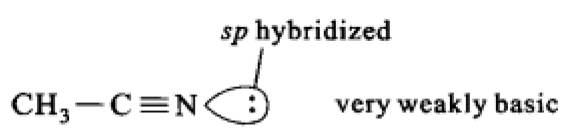
Hybridization Effects Our study of terminal alkynes showed that electrons are held more tightly by orbitals with more *s* character. This principle helps to explain why unsaturated amines tend to be weaker bases than simple aliphatic amines. In pyridine, for example, the nonbonding electrons occupy an sp^2 orbital, with greater *s* character and more tightly held electrons than those in the sp^3 orbital of an aliphatic amine. Pyridine's nonbonding electrons are less available for bonding to a proton. Pyridine does not lose its aromaticity on protonation, however, and it is a much stronger base than pyrrole.



pyridine, $pK_b = 8.75$
(吡啶)

piperidine, $pK_b = 2.88$
(哌啶)

The effect of increased *s* character on basicity is even more pronounced in nitriles with *sp* hybridization. For example, acetonitrile has a pK_b of 24, showing that it is a very weak base. In fact, a concentrated mineral acid is required to protonate acetonitrile.



$pK_b = 24$

PROBLEM 20-3

Rank each set of compounds in order of increasing basicity.

(a) NaOH, NH_3, CH_3NH_2, Ph—NH_2
(b) aniline, *p*-methylaniline, *p*-nitroaniline
(c) aniline, pyrrole, pyridine
(d) pyrrole, imidazole, 3-nitropyrrole

20-6 Salts of Amines

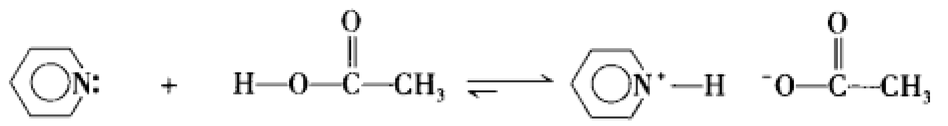
Protonation of an amine gives an **amine salt.** The amine salt is composed of two types of ions: the protonated amine cation (an ammonium ion) and the anion derived from the acid. Simple amine salts are named as the substituted **ammonium salts.** Salts of complex amines use the names of the amine and the acid that make up the salt.

$$\underset{n\text{-propylamine}}{CH_3CH_2CH_2—\ddot{N}H_2} + \underset{\text{hydrochloric acid}}{HCl} \rightleftharpoons \underset{n\text{-propylammonium chloride}}{CH_3CH_2CH_2—NH_3^+ \ ^-Cl}$$

(氯化正丙铵)

$$\underset{\text{triethylamine}}{(CH_3CH_2)_3N:} + \underset{\text{sulfuric acid}}{H_2SO_4} \rightleftharpoons \underset{\text{triethylammonium hydrogen sulfate}}{(CH_3CH_2)_3NH^+ HSO_4^-}$$

(硫酸氢化三乙基铵)



pyridine + acetic acid ⇌ pyridinium acetate (吡啶乙酸盐)

Amine salts are ionic, high-melting, nonvolatile solids. They are much more soluble in water than the parent amines, and they are only slightly soluble in nonpolar organic solvents.

Formation of amine salts can be used to isolate and characterize amines. Most amines containing more than six carbon atoms are relatively insoluble in water. In dilute aqueous acid, these amines form their corresponding ammonium salts, and they dissolve. Formation of a soluble salt is one of the characteristic functional group tests for amines.

$$\underset{\substack{\text{"free" amine} \\ \text{(water insoluble)}}}{R_3N:} \underset{\text{aq.NaOH}}{\overset{\text{aq.HCl}}{\rightleftharpoons}} \underset{\substack{\text{amine salt} \\ \text{(water soluble)}}}{R_3\overset{+}{N}H\ ^-Cl:}$$

The formation of amine salts is also used to separate amines from less basic compounds (Figure 20-6). In dilute acid, the amine forms a salt and dissolves. When the solution is made alkaline (by the addition of NaOH), the free amine is regenerated. The purified free amine either separates out of the aqueous solution or is extracted into an organic solvent.

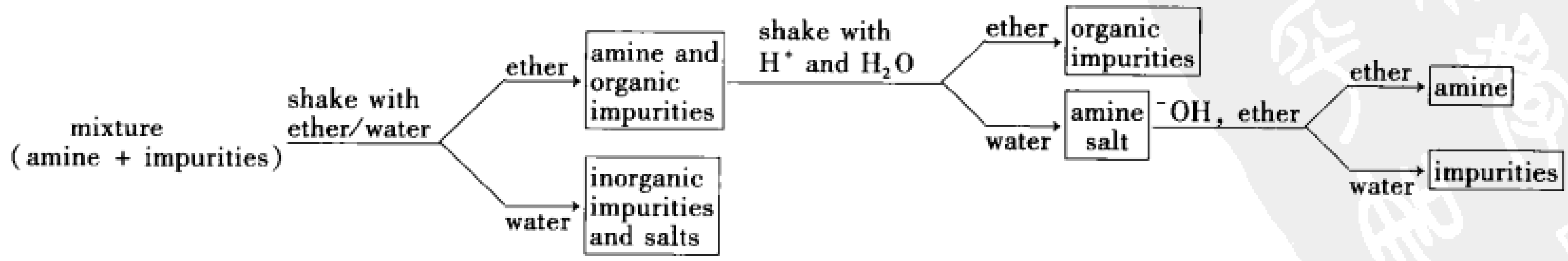


Figure 20-6 The basicity of an amine can be used for purification. The amine is initially more soluble in ether than in water. Addition of dilute HCl converts it to the water-soluble hydrochloride salt. Neutralization with NaOH regenerates the free amine.

Many drugs and other biologically important amines are commonly stored and used as their salts. Amine salts are less prone to decomposition by oxidation and other reactions, and they have virtually no fishy odor. The salts are soluble in water, and they are easily converted to solutions for syrups and injectables.

20−7 Amine Salts as Phase-Transfer Catalysts

Quaternary ammonium salts ($R_4N^+ \ ^-X$) are especially useful because they are somewhat soluble in both water and nonpolar organic solvents. They work as **phase-transfer catalysts** to move ionic reagents into organic solvents in which they would not otherwise dissolve. As an example, consider the reaction shown in Figure 20−7. This reaction generates dichlorocarbene ($:CCl_2$) by alpha elimination using sodium hydroxide. Dichlorocarbene adds to cyclohexene to form a new cyclopropane ring.

The flask pictured on the left in Figure 20−7 shows the reaction before adding a phase-transfer catalyst. Water forms the upper layer, and chloroform forms the lower layer. Sodium hydroxide dissolves in water but not in chloroform, so it is entirely in the water layer. Cyclohexene dissolves in chloroform but not in water, so it is entirely in the chloroform layer. Very little reaction occurs under these conditions, even when using a high-speed stirrer.

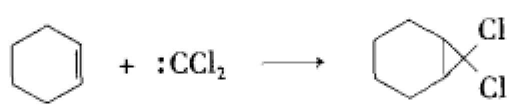
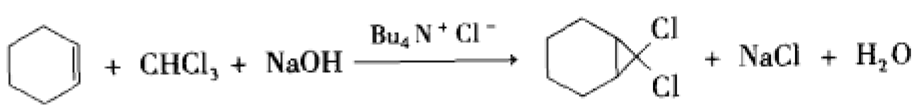


Figure 20−7 Use of a phase-transfer catalyst. This example shows the reaction of cyclohexene and chloroform, both insoluble in water, with a 50% aqueous solution of sodium hydroxide.

The flask pictured on the right shows the reaction after tetrabutylammonium chloride, a phase-transfer catalyst, is added. The tetrabutylammonium ion forms an ion pair with hydroxide ion. This ion pair has large alkyl groups that enhance its solubility in organic solvents, so it can migrate (aided by high-speed stirring) into the chloroform layer. In the organic phase, hydroxide ion is more reactive than in the aqueous phase because it is stripped of its solvating water molecules. Hydroxide reacts with chloroform to give dichlorocarbene, which reacts with cyclohexene to give the cyclopropanated product.

Overall reaction



(80%)

Mechanism

1. Aqueous phase

$$Bu_4N^+ \ ^-Cl + Na^+ \ ^-OH \rightleftharpoons Bu_4N^+ \ ^-OH + Na^+ \ ^-Cl$$

tetrabutylammonium chloride (ion pair)

2. Organic phase

$$Bu_4N^+ \ ^-OH + CHCl_3 \rightleftharpoons Bu_4N^+ \ ^-CCl_3 + H_2O$$

organic soluble

$$Bu_4N^+ \ ^-CCl_3 \rightleftharpoons Bu_4N^+ \ ^-Cl + :CCl_2$$

catalyst regenerated dichlorocarbene(二氯卡宾)

Other anions may be transferred into organic phases by tetra-alkylammonium phase-transfer catalysts. For

example, sodium cyanide (NaCN) is not soluble in most organic solvents, but the cyanide ion (^-CN) can be used as a nucleophile in organic solvents under phase-transfer conditions, as shown here. Like the hydroxide ion, cyanide is a stronger nucleophile in the organic phase because it is not solvated by water molecules.

$$\underset{}{Bu_4N^+\,^-Cl} + \underset{\text{organic insoluble}}{Na^+\,^-CN} \rightleftharpoons Bu_4N^+\,^-CN + Na^+\,^-Cl \qquad \text{(aqueous phase)}$$

$$\underset{\text{organic soluble}}{Bu_4N^+\,^-CN} + R{-}CH_2{-}Cl \longrightarrow \underset{\text{a nitrile(腈)}}{R{-}CH_2{-}C{\equiv}N} + Bu_4N^+\,^-Cl \qquad \text{(organic phase)}$$

20-8 Spectroscopy of Amines

20-8A Infrared Spectroscopy

The most reliable IR absorption of primary and secondary amines is the N—H stretch whose frequency appears between 3 200 and 3 500 cm^{-1}. Since this absorption is often broad, it is easily confused with the O—H absorption of an alcohol. In most cases, however, one or more spikes are visible in the N—H stretching region of an amine spectrum. Primary amines ($R{-}NH_2$) usually give two N—H spikes, and secondary amines ($R_2N{-}H$) usually give just one. Tertiary amines (R_3N) give no N—H absorptions.

Although an amine IR spectrum also contains absorptions resulting from vibrations of C—N bonds, these vibrations appear around 1 000 to 1 200 cm^{-1}, in the same region as C—C and C—O vibrations. Therefore, they are not very useful for identifying an amine.

20-8B Proton NMR Spectroscopy

Like the O—H protons of alcohols, the N—H protons of amines absorb at chemical shifts that depend on the extent of hydrogen bonding. The solvent and the sample concentration influence hydrogen bonding and therefore the chemical shift. Typical N—H chemical shifts appear in the range $\delta 1$ to $\delta 4$.

Another similarity between O—H and N—H protons is their failure, in many cases, to show spin-spin splitting. In some samples, N—H protons exchange from one molecule to another at a rate that is faster than the time scale of the NMR experiment, and the N—H protons fail to show magnetic coupling. Sometimes the N—H protons of a very pure amine will show clean splitting, but these cases are rare. More commonly, the N—H protons appear as broad peaks. A broad peak should arouse suspicion of N—H protons. As with O—H protons, an absorption of N—H protons decreases or disappears after shaking the sample with D_2O.

Nitrogen is not as electronegative as oxygen and the halogens, so the protons on the α-carbon atoms of amines are not as strongly deshielded. Protons on an amine's α-carbon atom generally absorb between $\delta 2$ and $\delta 3$, but the exact position depends on the structure and substitution of the amine.

$$\underset{\text{methyl } \delta 2.3}{\overset{\downarrow}{CH_3}{-}NR_2} \qquad \underset{\text{methylene } \delta 2.7}{R{-}\overset{\downarrow}{CH_2}{-}NR_2} \qquad \underset{\text{methine } \delta 2.9}{R_2\overset{\downarrow}{CH}{-}NR_2}$$

20-8C Carbon NMR Spectroscopy

The α-carbon atom bonded to the nitrogen of an amine usually shows a chemical shift of about 30 to 50. This

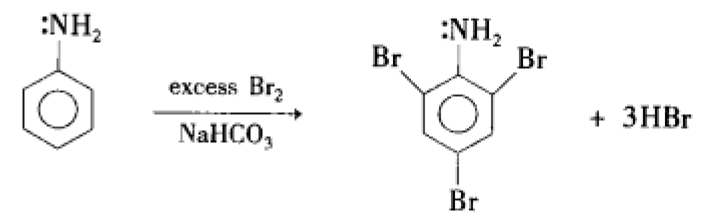
range agrees with our general rule that a carbon atom shows a chemical shift about 20 times as great as the protons bonded to it.

20-9 Aromatic Substitution of Arylamines and Pyridine

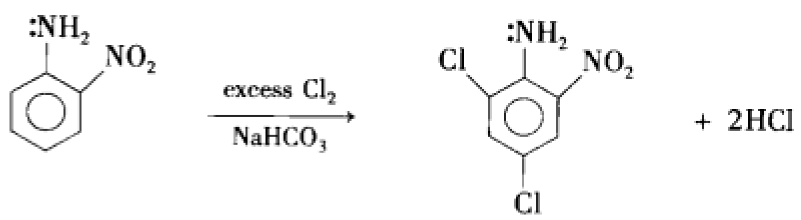
20-9A Electrophilic Aromatic Substitution of Arylamines

In an arylamine, the nonbonding electrons on nitrogen help stabilize intermediates resulting from electrophilic attack at the positions ortho or para to the amine substituent. As a result, amino groups are strong activating groups and ortho, para-directors.

The following reactions show halogenation of aniline derivatives, which occurs readily without a catalyst. If an excess of the reagent is used, all the unsubstituted positions ortho and para to the amino group become substituted.

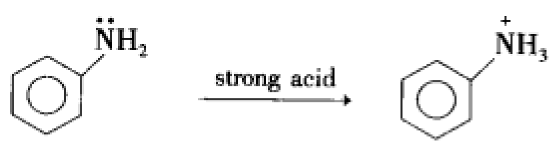


aniline 2,4,6-tribromoaniline

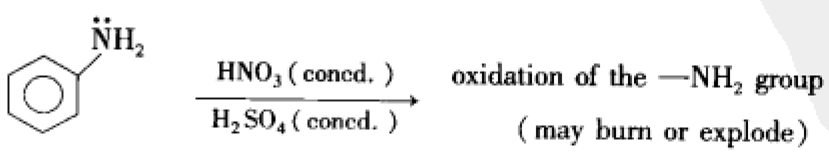


o-nitroaniline 4,6-dichloro-2-nitroaniline

Care must be exercised in reactions with aniline derivatives, however. Strongly acidic reagents protonate the amino group, giving an ammonium salt that bears a full positive charge. The $—NH_3^+$ group is strongly deactivating (and meta-allowing). Therefore, strongly acidic reagents are unsuitable for substitution of anilines. Oxidizing acids (such as nitric and sulfuric acids) may oxidize the amino group, leading to decomposition and occasional violent reactions.



activated deactivated



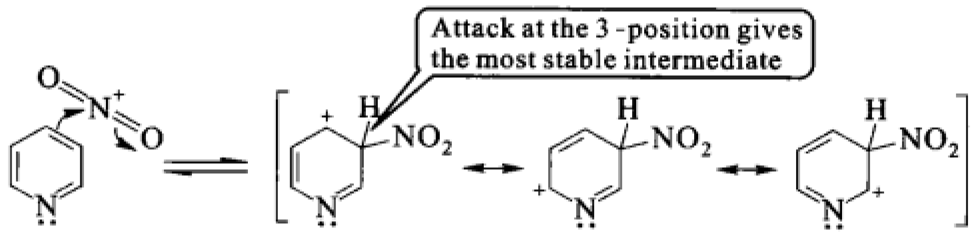
20-9B Electrophilic Aromatic Substitution of Pyridine

In its aromatic substitution reactions, pyridine resembles a strongly deactivated benzene. Friedel-Crafts reactions fail completely, and other substitutions require unusually strong conditions. Deactivation results from the electron-withdrawing effect of the electronegative nitrogen atom. Its nonbonding electrons are perpendicular to the π

system, and they cannot stabilize the positively charged intermediate. When pyridine does react, it gives substitution at the 3-position, analogous to the meta substitution shown by deactivated benzene derivatives.

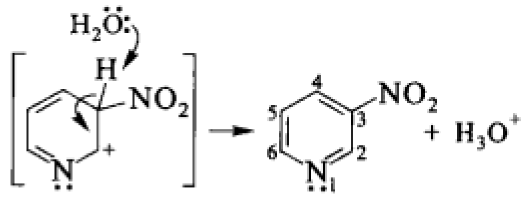
MECHANISM 20-1 Electrophilic Aromatic Substitution of Pyridine

***Step 1*:** Attack takes place at the 3-position.



pyridine (吡啶)

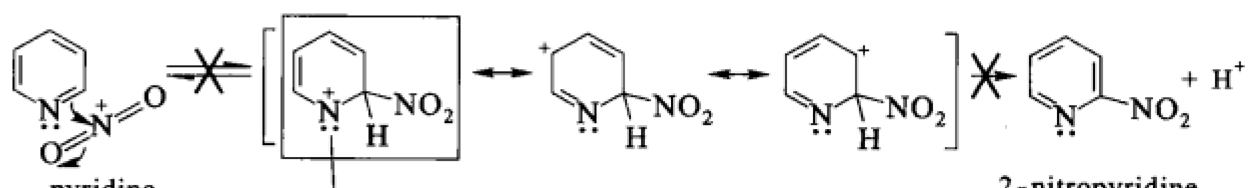
***Step 2*:** Loss of a proton gives the product.



3-nitropyridine
(observed)
(3-硝基吡啶)

In comparison, consider the intermediate that would be formed by attack at the 2-position:

Attack at the 2-position (not observed)



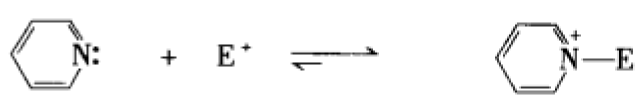
pyridine

no octet
unfavorable

2-nitropyridine
(not observed)

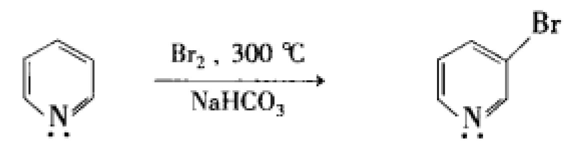
Electrophilic attack on pyridine at the 2-position gives an unstable intermediate, with one of the resonance structures showing a positive charge and only six electrons on nitrogen. In contrast, all three resonance forms of the intermediate from attack at the 3-position place the positive charge on the less electronegative carbon atoms.

Electrophilic substitution of pyridine is further hindered by the tendency of the nitrogen atom to attack electrophiles and take on a positive charge. The positively charged pyridinium ion is even more resistant than pyridine to electrophilic substitution.

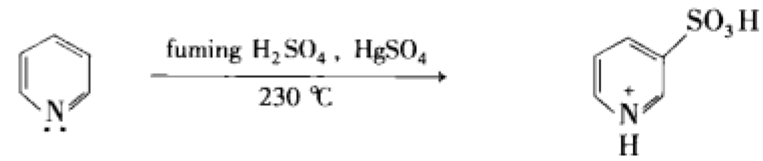


pyridine electrophile pyridinium ion (吡啶鎓离子)
(less reactive)

Two electrophilic substitutions of pyridine are shown here. Notice that these reactions require severe conditions, and the yields are poor to fair.



pyridine 3-bromopyridine (3－溴吡啶) (30%)



pyridine pyridine-3-sulfonic acid (3－吡啶磺酸) (protonated) (70%)

PROBLEM 20－4

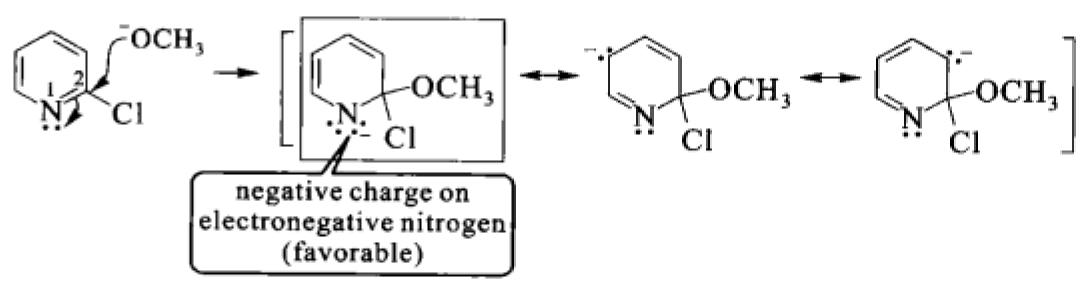
Propose a mechanism for the sulfonation of pyridine, pointing out why sulfonation occurs at the 3-position.

20－9C Nucleophilic Aromatic Substitution of Pyridine

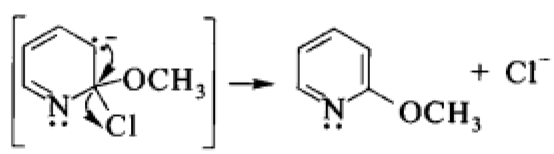
Pyridine is deactivated toward electrophilic attack, but it is activated toward attack by electron-rich nucleophiles; that is , it is activated toward nucleophilic aromatic substitution. If there is a good leaving group at either the 2-position or the 4-position, a nucleophile can attack and displace the leaving group. The following reaction shows nucleophilic attack at the 2-position. The intermediate is stabilized by delocalization of the negative charge onto the electronegative nitrogen atom. This stabilization is not possible if attack occurs at the 3-position.

MECHANISM 20－2 Nucleophilic Aromatic Substitution of Pyridine

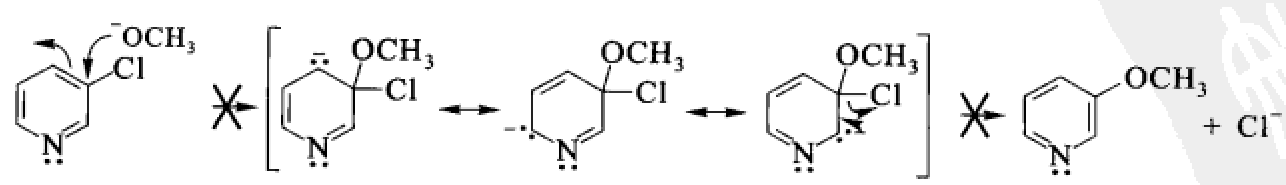
Step 1: Nucleophilic attack at the 2-position (or the 4-position) forms a stabilized intermediate.



Step 2: Expulsion of the leaving group gives the product.



Nucleophilic attack at the 3-position (not observed)



(no delocalization of negative charge onto N)

PROBLEM 20-5

We have considered nucleophilic aromatic substitution of pyridine at the 2-position and 3-position but not at the 4-position. Complete the three possible cases by showing the mechanism for the reaction of methoxide ion with 4-chloropyridine.

PROBLEM 20-6

(a) Propose a mechanism for the reaction of 2-bromopyridine with sodium amide to give 2-aminopyridine.

(b) When 3-bromopyridine is used in this reaction, stronger reaction conditions are required and a mixture of 3-aminopyridine and 4-aminopyridine results. Propose a mechanism to explain this curious result.

20-10 Alkylation of Amines by Alkyl Halides

Amines react with primary alkyl halides to give alkylated ammonium halides. Alkylation proceeds by the S_N2 mechanism, so it is not feasible with tertiary halides because they are too hindered. Secondary halides often give poor yields, with elimination predominating over substitution.

$$\underset{\text{primary amine}}{R-\ddot{N}H_2} + \underset{\text{primary halide}}{R'-CH_2-Br} \longrightarrow \underset{\text{salt of a secondary amine}}{R-\overset{+}{N}H_2-CH_2-R'\ ^-Br}$$

Unfortunately, the initially formed salt may become deprotonated. The resulting secondary amine is nucleophilic, and it can react with another molecule of the halide.

$$R-\overset{+}{N}H_2-CH_2-R'\ ^-Br + R-\ddot{N}H_2 \rightleftharpoons \underset{2^\circ\ \text{amine}}{R-\ddot{N}H-CH_2-R'} + R-\overset{+}{N}H_3\ ^-Br$$

$$\underset{2^\circ\ \text{amine}}{R-\ddot{N}H-CH_2-R'} + R'-CH_2-Br \longrightarrow \underset{\text{salt of a tertiary amine}}{R-\overset{+}{N}H(CH_2-R')-CH_2-R'\ ^-Br}$$

The disadvantage of direct alkylation lies in stopping it at the desired stage. Even if just one equivalent of the halide is added, some amine molecules will react once, some will react twice, and some will react three times (to give the tetraalkylammonium salt). Others will not react at all. A complex mixture results.

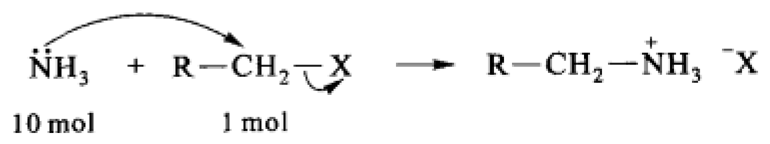
Alkylation of amines can give good yields of the desired alkylated products in two types of reactions:

1. "*Exhaustive*" *alkylation to the tetraalkylammonium salt.* Mixtures of different alkylated products are avoided if enough alkyl halide is added to alkylate the amine as many times as possible. This **exhaustive alkylation** gives a tetraalkylammonium salt. A mild base (often $NaHCO_3$ or dilute NaOH) is added to deprotonate the intermediate alkylated amines and to neutralize the large quantities of HX formed.

$$CH_3CH_2CH_2-NH_2 + 3CH_3-I \xrightarrow{NaHCO_3} \underset{(90\%)}{CH_3CH_2CH_2-\overset{+}{N}(CH_3)_3\ ^-I}$$

2. *Reaction with a large excess of ammonia.* Because ammonia is inexpensive and has a low molecular weight, it is convenient to use a very large excess. Addition of a primary alkyl halide to a large excess of ammonia forms the primary amine, and the probability of dialkylation is small. Excess ammonia is simply allowed to

evaporate.



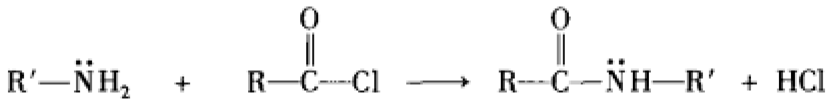
PROBLEM 20-7

Show how you would use direct alkylation to synthesize the following compounds.

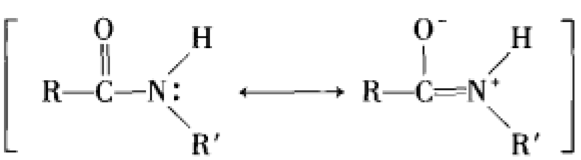
(a) benzyltrimethylammonium iodide (b) 1-pentanamine (c) benzylamine

20-11 Acylation of Amines by Acid Chlorides

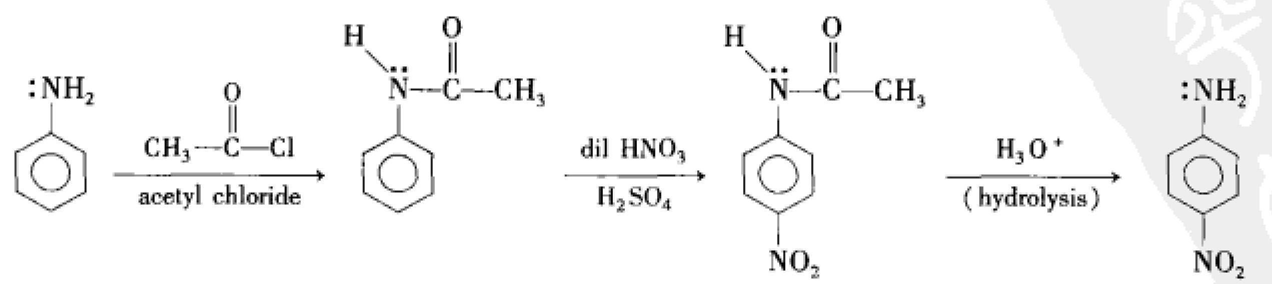
Primary and secondary amines react with acid halides to form amides. This reaction is a *nucleophilic acyl substitution*: the replacement of a leaving group on a carbonyl carbon by a nucleophile. We will study nucleophilic acyl substitution in detail in Chapter 21. In this case, the amine replaces chloride ion.



The amide produced in this reaction usually does not undergo further acylation. Amides are stabilized by a resonance structure that involves nitrogen's nonbonding electrons and places a positive charge on nitrogen. As a result, amides are much less basic and less nucleophilic than amines.



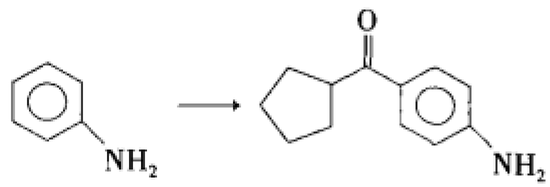
The diminished basicity of amides can be used to advantage in electrophilic aromatic substitutions. For example, if the amino group of aniline is acetylated to give acetanilide, the resulting amide is still activating and ortho, para-directing. Unlike aniline, however, acetanilide may be treated with acidic (and mild oxidizing) reagents, as shown next. Aryl amino groups are frequently acylated before further substitutions are attempted on the ring, and the acyl group is removed later by acidic or basic hydrolysis.



aniline (苯胺) acetanilide (乙酰苯胺) *p*-nitroaniline (对硝基苯胺)

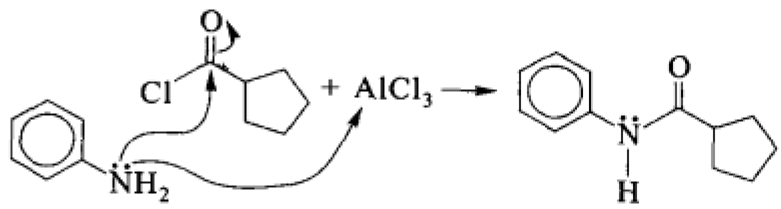
SOLVED PROBLEM 20-1

Show how you would accomplish the following synthetic conversion in good yield.

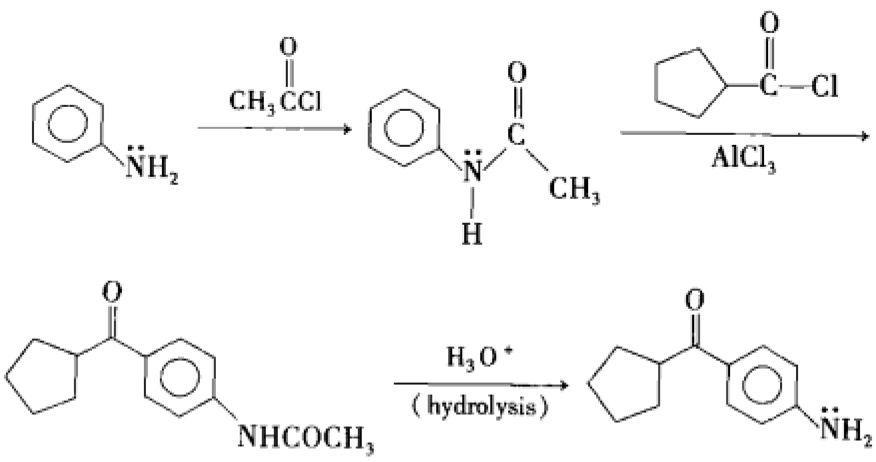


SOLUTION

An attempted Friedel-Crafts acylation on aniline would likely meet with disaster. The free amino group would attack both the acid chloride and the Lewis acid catalyst.

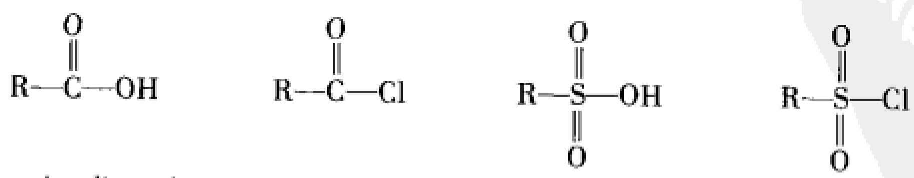


We can control the nucleophilicity of aniline's amino group by converting it to an amide, which is still activating and ortho, para-directing for the Friedel-Crafts reaction. Acylation, followed by hydrolysis of the amide, gives the desired product.



20-12 Formation of Sulfonamides

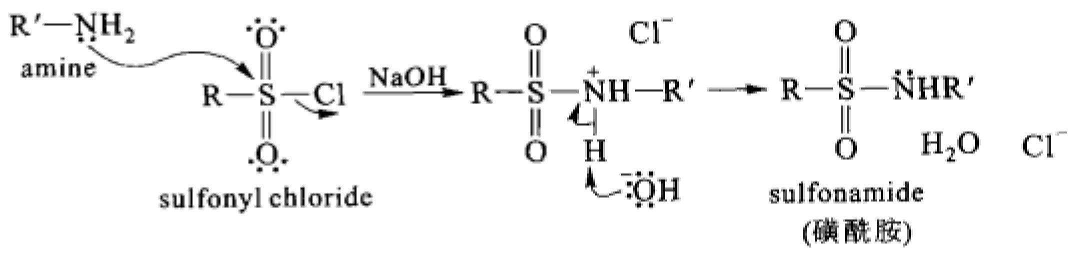
Sulfonyl chlorides are the acid chlorides of sulfonic acids. Like acyl chlorides, sulfonyl chlorides are strongly electrophilic.



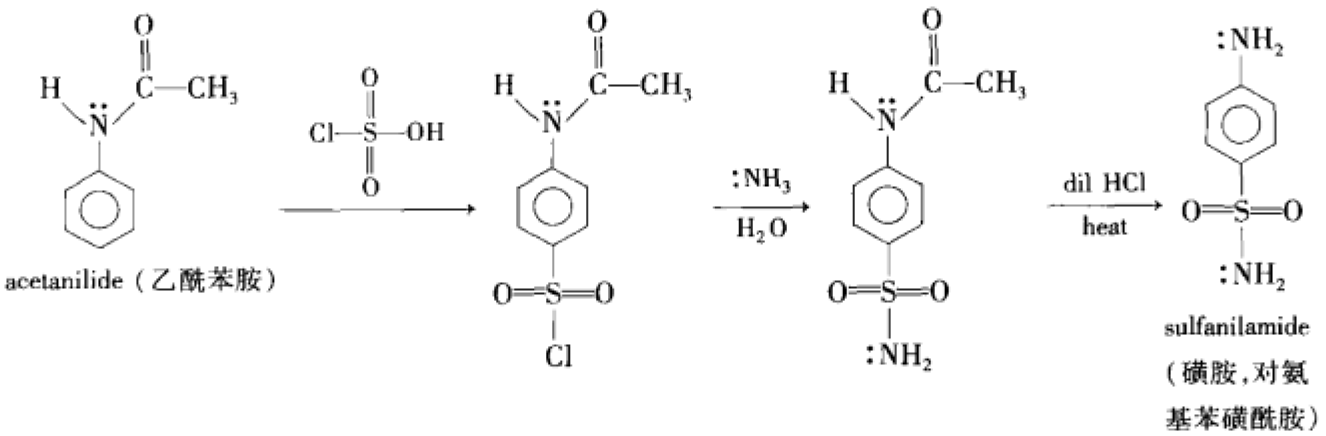
a carboxylic acid (羧酸) | an acyl chloride (acid chloride) (酰氯) | a sulfonic acid (磺酸) | a sulfonyl chloride (磺酰氯)

A primary or secondary amine attacks a sulfonyl chloride and displaces chloride ion to give an amide. Amides of sulfonic acids are called **sulfonamides.** This reaction is similar to the formation of a sulfonate ester from a sulfonyl chloride (such as tosyl chloride) and an alcohol.

The *sulfa drugs* are a class of sulfonamides used as antibacterial agents. In 1936, sulfanilamide was found to



be effective against streptococcal infections. Sulfanilamide is synthesized from acetanilide (having the amino group protected as an amide) by chlorosulfonation followed by treatment with ammonia. The final reaction is hydrolysis of the protecting group to give sulfanilamide.



PROBLEM 20-8

What would happen in the synthesis of sulfanilamide if the amino group were not protected as an amide in the chlorosulfonation step?

20-13 Amines as Leaving Groups: The Hofmann Elimination

Amines can be converted to alkenes by elimination reactions, much like alcohols and alkyl halides undergo elimination to give alkenes. An amine cannot undergo elimination directly, however, because the leaving group would be an amide ion ($^-NH_2$ or ^-NHR), which is a very strong base and a poor leaving group. An amino group can be converted to a good leaving group by exhaustive methylation, which converts it to a quaternary ammonium salt that can leave as a neutral amine. Exhaustive methylation is usually accomplished using methyl iodide.

Exhaustive methylation of an amine

$$R-\underset{\text{poor leaving group}}{\ddot{N}H_2} + 3CH_3-I \longrightarrow R-\underset{\text{good leaving group}}{\overset{+}{N}(CH_3)_3}\ ^-I + 2HI$$

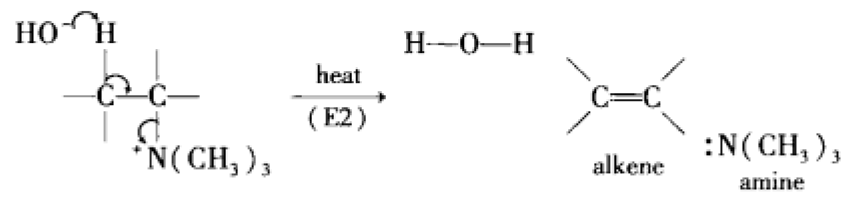
Elimination of the quaternary ammonium salt generally takes place by the E2 mechanism, which requires a strong base, To provide the base, the quaternary ammonium iodide is converted to the hydroxide salt by treatment with silver oxide. Heating of the quaternary ammonium hydroxide results in E2 elimination and formation of an alkene. This elimination of a quaternary ammonium hydroxide is called the **Hofmann elimination.**

Conversion to the hydroxide salt

$$\underset{\text{quaternary ammonium iodide}}{R{-}\overset{+}{N}(CH_3)_3\ {}^{-}I} + \frac{1}{2}Ag_2O + H_2O \longrightarrow \underset{\substack{\text{quaternary ammonium hydroxide}\\ (\text{季铵碱})}}{R{-}\overset{+}{N}(CH_3)_3\ {}^{-}OH} + AgI$$

MECHANISM 20−3 Hofmann Elimination

The Hofmann elimination is a one-step, concerted E2 reaction using an amine as the leaving group.

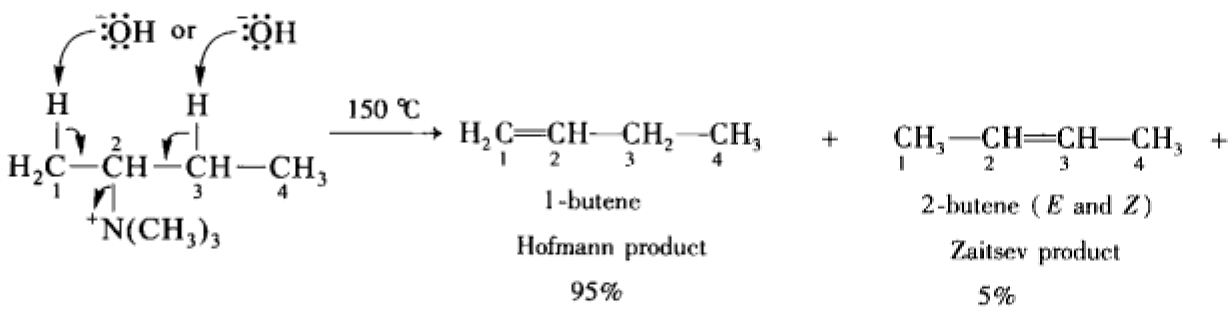


For example, when 2-butanamine is exhaustively methylated, converted to the hydroxide salt, and heated, elimination takes place to form a mixture of 1-butene and 2-butene.

Exhaustive methylation and conversion to the hydroxide salt

$$\underset{\text{2-butanamine}}{\overset{1}{C}H_3{-}\overset{2}{C}H(:NH_2){-}\overset{3}{C}H_2{-}\overset{4}{C}H_3} \xrightarrow[(2)\ Ag_2O,\ H_2O]{(1)\ \text{excess } CH_3I} \underset{\text{quaternary ammonium hydroxide(季铵碱)}}{\overset{1}{C}H_3{-}\overset{2}{C}H(\overset{+}{N}(CH_3)_3){-}\overset{3}{C}H_2{-}\overset{4}{C}H_3\ \ {}^{-}OH}$$

Heating and Hofmann elimination



We saw that eliminations of alkyl halides usually follow the Zaitsev's rule; that is, the most substituted product predominates. This rule applies because the most-substituted alkene is usually the most stable. In the Hofmann elimination, however, the product is commonly the *least*-substituted alkene. We often classify an elimination as giving mostly the *Zaitsev product* (the most-substituted alkene) or the *Hofmann product* (the least-substituted alkene).

Zaitsev elimination

$$\underset{\text{2-chlorobutane}}{\overset{1}{C}H_3{-}\overset{2}{C}H(Cl){-}\overset{3}{C}H_2{-}\overset{4}{C}H_3} + \underset{\text{sodium methoxide}}{Na^{+}\ {}^{-}OCH_3} \longrightarrow \underset{\substack{\text{2-butene}(E \text{ and } Z)\\ \text{Zaitsev product}\\ (67\%)}}{\overset{1}{C}H_3{-}\overset{2}{C}H{=}\overset{3}{C}H{-}\overset{4}{C}H_3} + \underset{\substack{\text{1-butene}\\ \text{Hofmann product}\\ (33\%)}}{H_2\overset{1}{C}{=}\overset{2}{C}H{-}\overset{3}{C}H_2{-}\overset{4}{C}H_3}$$

The Hofmann elimination's preference for the least-substituted alkene stems from several factors, but one of the most compelling involves the sheer bulk of the leaving group. Remember that the E2 mechanism requires an anti-coplanar arrangement of the proton and the leaving group. The extremely large trialkylamine leaving group in the Hofmann elimination often interferes with this coplanar arrangement.

Figure 20−8 shows the stereochemistry of the Hofmann elimination of 2-butanamine. The methylated ammonium salt eliminates by losing trimethylamine and a proton on either C1 or C3. The possible conformations along

the C2—C3 bond are shown at the top of Figure 20−8. An anti-coplanar arrangement between a C3 proton and the leaving group requires an unfavorable gauche interaction between the C4 methyl group and the bulky trimethylammonium group. The most-stable conformation about the C2—C3 bond has a methyl group in the anti-coplanar position, preventing elimination along the C2—C3 bond.

The bottom half of Figure 20−8 shows the conformations along the C1—C2 bond. *Any* of the three staggered conformations of the C1—C2 bond provides an anti relationship between one of the protons and the leaving group. The Hofmann product predominates because elimination of one of the C1 protons involves a lower-energy, more probable transition state than the crowded transition state required for Zaitsev (C2—C3) elimination.

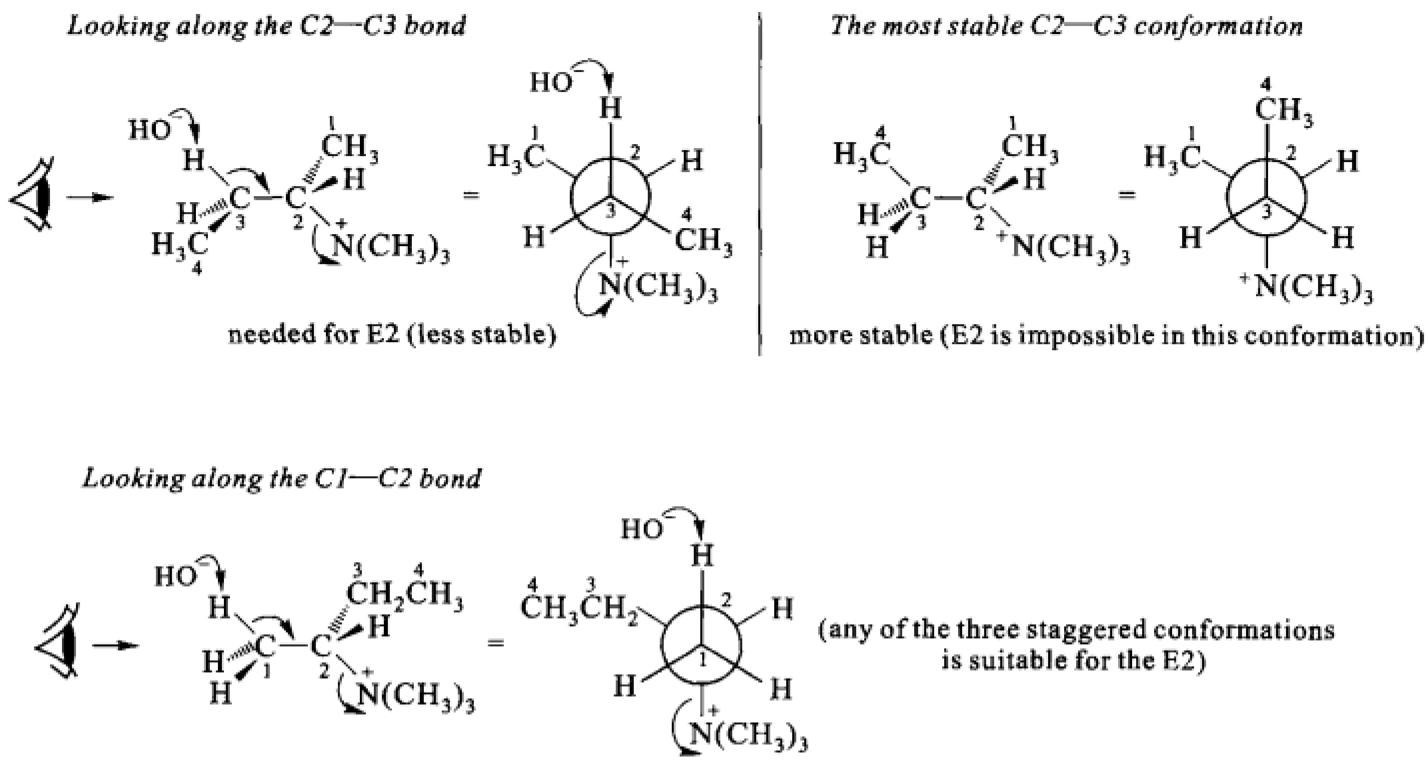


Figure 20−8 Hofmann elimination of 2-butanamine. The most stable conformation of the C2—C3 bond has no proton on C3 in an anti relationship to the leaving group. Along the C1—C2 bond, however, any staggered conformation has an anti relationship between a proton and the leaving group. Abstraction of a proton from C1 gives the Hofmann product.

The Hofmann elimination is frequently used to determine the structures of complex amines by converting them to simpler amines. The direction of elimination is usually predictable, giving the least-substituted alkene. Figure 20−9 shows two examples using the Hofmann elimination to simplify complex amines.

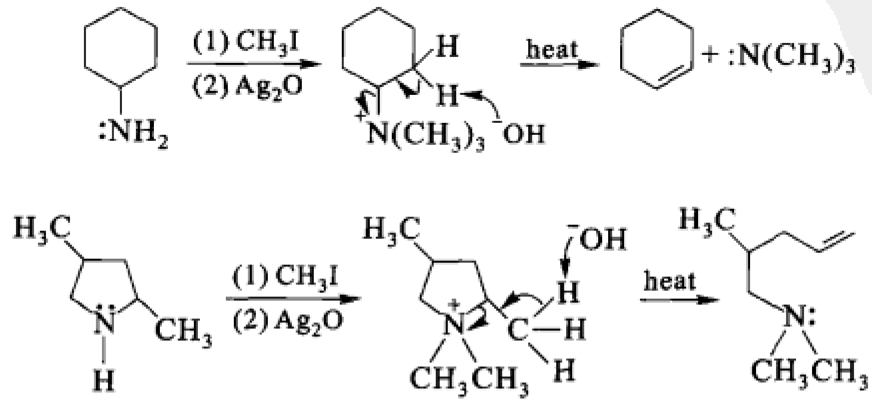
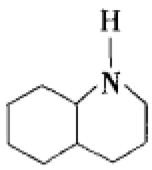
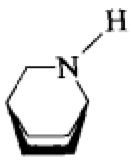


Figure 20−9 Examples of the Hofmann elimination. The least-substituted alkene is usually the favored product.

PROBLEM 20-9

Predict the major products formed when the following amines undergo exhaustive methylation, treatment with Ag_2O, and heating.

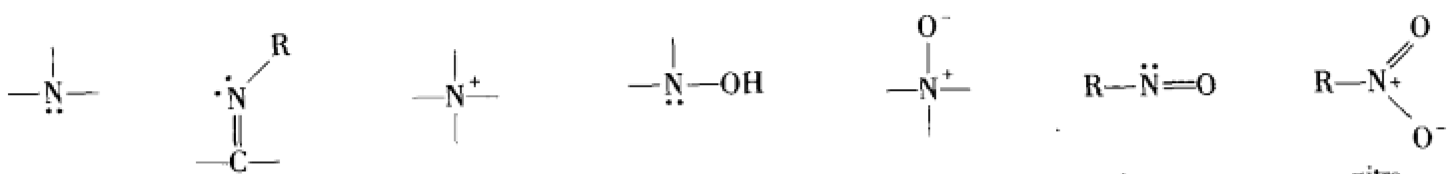
(a) 2-hexanamine (b) 2-methylpiperidine (c) *N*-ethylpiperidine

(d)  (e)  (f)

20-14 Oxidation of Amines; The Cope Elimination

Amines are notoriously easy to oxidize, and oxidation is often a side reaction in amine syntheses. Amines also oxidize during storage in contact with the air. Preventing air oxidation is one of the reasons for converting amines to their salts for storage or use as medicines.

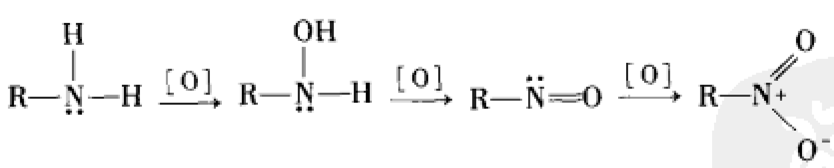
The following partial structures show some of the bonding and oxidation states of amines:



amine (胺) imine (亚胺) ammonium salt (铵盐) hydroxylamine (羟胺) amine oxide (氧化胺) nitroso (亚硝基) nitro (硝基)

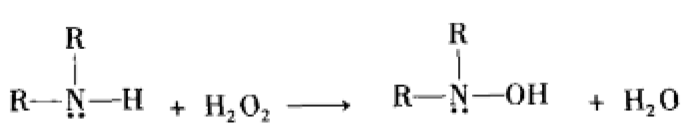
Depending on their specific structures, these states are generally more oxidized as you go from left to right. (Note the increasing number of bonds to oxygen.)

Most amines are oxidized by common oxidants such as H_2O_2, permanganate, and peroxyacids. Primary amines oxidize easily, but complex mixtures of products often result. The following sequence shows increasingly oxidized products of a primary amine, as it becomes more oxidized from left to right. The symbol [O] is used for a generic oxidizing agent.



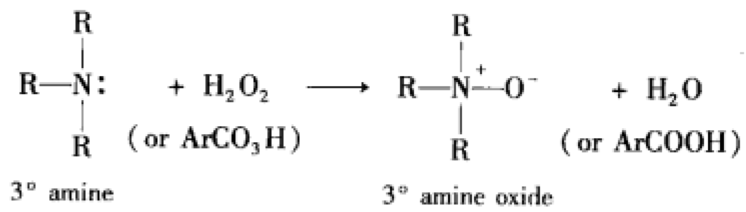
1° amine hydroxylamine nitroso nitro

Secondary amines are easily oxidized to **hydroxylamines.** Side products are often formed, however, and the yields may be low. The mechanisms of amine oxidations are not well characterized, partly because many reaction paths (especially those involving free radicals) are available.



2° amine a 2° hydroxylamine

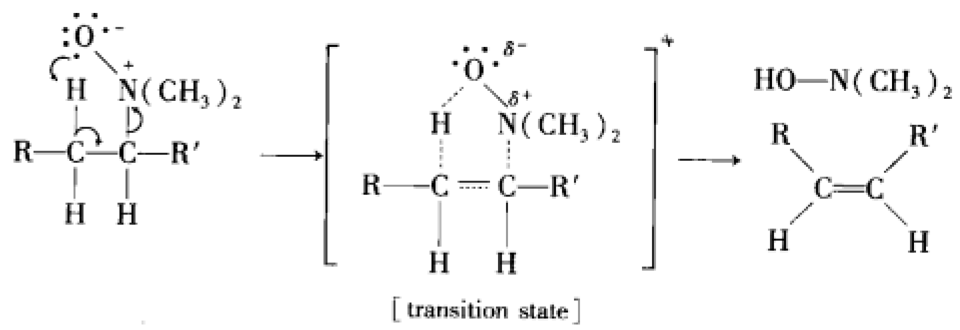
Tertiary amines are oxidized to **amine oxides**, often in good yields. Either H_2O_2 or a peroxyacid may be used for this oxidation. Notice that an amine oxide must be drawn with a full positive charge on nitrogen and a negative charge on oxygen, as in nitro compounds. Because the N—O bond of the amine oxide is formed by donation of the electrons on nitrogen, this bond is often written as an arrow (N→O) in older literature.



Because of the positive charge on nitrogen, the amine oxide may undergo a **Cope elimination**, much like the Hofmann elimination of a quaternary ammonium salt. The amine oxide acts as its own base through a cyclic transition state, so a strong base is not needed. The Cope elimination generally gives the same orientation as Hofmann elimination, resulting in the least-substituted alkene.

MECHANISM 20-4 The Cope Elimination of an Amine Oxide

The Cope elimination is a one-step, concerted E2 reaction using an amine oxide as both the base and the leaving group. Syn stereochemistry is required for the Cope elimination.



Cope elimination occurs under milder conditions than Hofmann elimination. It is particularly useful when a sensitive or reactive alkene must be synthesized by the elimination of an amine. Because the Cope elimination involves a cyclic transition state, it occurs with syn stereochemistry.

PROBLEM 20-10

Give the products expected when the following tertiary amines are treated with a peroxyacid and heated.

(a) *N*,*N*-dimethyl-2-hexanamine (b) *N*,*N*-diethyl-2-hexanamine

(c) cyclohexyldimethylamine (d) *N*-ethylpiperidine

20-15 Reactions of Amines with Nitrous Acid

Reactions of amines with nitrous acid (H—O—N=O) are particularly useful for synthesis. Because nitrous acid is unstable, it is generated in situ (in the reaction mixture) by mixing sodium nitrite ($NaNO_2$) with cold, dilute hydrochloric acid.

$$Na^+ \ {}^-:\ddot{O}—\ddot{N}=\dot{O}: \ + \ H^+Cl^- \rightleftharpoons \ H—\ddot{O}—\ddot{N}=\dot{O}: \ + \ Na^+Cl^-$$

sodium nitrite (亚硝酸钠) nitrous acid (亚硝酸)

Reaction with Primary Amines: Formation of Diazonium Salts Primary amines react with nitrous acid, via the nitrosonium ion, to give diazonium cations of the form $R—\overset{+}{N}\equiv N$. This procedure is called **diazotization of an amine.** Diazonium salts are the most useful products obtained from the reactions of amines with nitrous acid.

$$\underset{\substack{\text{primary amine}\\(\text{伯胺})}}{R{-}\ddot{N}H_2} + \underset{\substack{\text{sodium nitrite}\\(\text{亚硝酸钠})}}{NaNO_2} + 2HCl \longrightarrow \underset{\text{diazonium salt (重氮盐)}}{R{-}\overset{+}{N}{\equiv}N\ Cl^-} + 2H_2O + NaCl$$

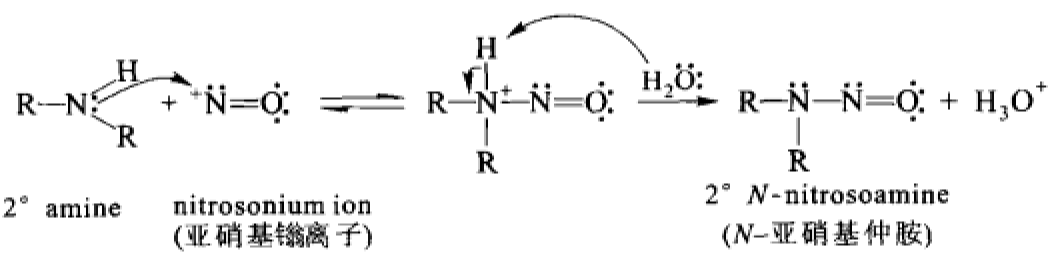
Alkanediazonium salts are unstable. They decompose to give nitrogen and carbocations.

$$\underset{\substack{\text{alkanediazonium cation}\\(\text{烷基重氮正离子})}}{R{-}\overset{+}{N}{\equiv}N:} \longrightarrow \underset{\text{carbocation}}{R^+} + \underset{\text{nitrogen}}{:N{\equiv}N:}$$

The driving force for this reaction is the formation of N_2, an exceptionally stable molecule. The carbocations generated in this manner react like others we have seen: by nucleophilic attack to give substitution, by proton loss to give elimination, and by rearrangement. Because of the many competing reaction pathways, alkanediazonium salts usually decompose to give complex mixtures of products. Therefore, the diazotization of primary alkylamines is not widely used for synthesis.

Arenediazonium salts (formed from arylamines) are relatively stable, however, and they serve as intermediates in a variety of important synthetic reactions. These reactions are discussed in Section 20−16.

Reaction with Secondary Amines: Formation of *N*-Nitrosoamines Secondary amines react with the nitrosonium ion to form secondary ***N*-nitrosoamines**, sometimes called *nitrosamines*.



Secondary *N*-nitrosoamines are stable under the reaction conditions because they do not have the N—H proton needed for the tautomerism to form a diazonium ion. The secondary *N*-nitrosoamine usually separates from the reaction mixture as an oily liquid.

Small quantities of *N*-nitrosoamines have been shown to cause cancer in laboratory animals. These findings have generated concern about the common practice of using sodium nitrite to preserve meats such as bacon, ham, and hot dogs. When the meat is eaten, sodium nitrite combines with stomach acid to form nitrous acid, which can convert amines in the food to *N*-nitrosoamines. Because nitrites are naturally present in many other foods, it is unclear just how much additional risk is involved in using sodium nitrite to preserve meats. More research is being done in this area to evaluate the risk.

The most useful reaction of amines with nitrous acid is the reaction of arylamines to form arenediazonium salts. We consider next how these diazonium salts may be used as synthetic intermediates.

PROBLEM 20−11

Predict the products from the reactions of the following amines with sodium nitrite in dilute HCl.

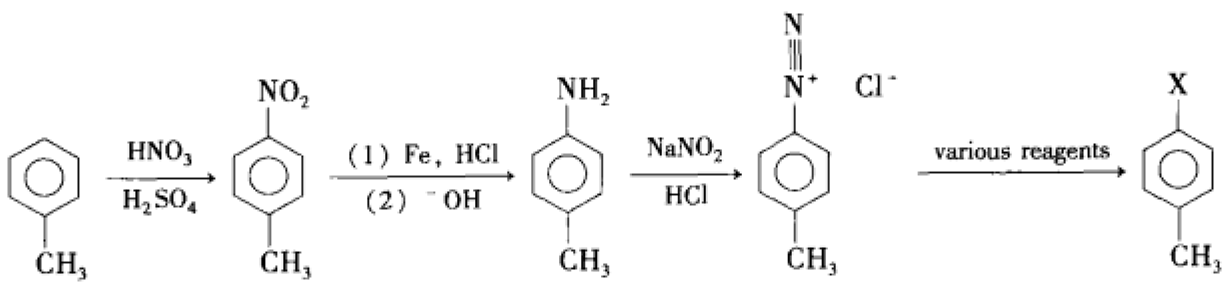
(a) cyclohexanamine (b) *N*-ethyl-2-hexanamine (c) piperidine (d) aniline

20−16 Reactions of Arenediazonium Salts

In contrast to alkanediazonium salts, arenediazonium salts are relatively stable in aqueous solutions around 0 to

10 ℃. Above these temperatures, they decompose, and they may explode if they are isolated and allowed to dry. The diazonium ($-\overset{+}{N}\equiv N$) group can be replaced by many different functional groups, including —H, —OH, —CN, and halogens.

Arenediazonium salts are formed by diazotizing a primary aromatic amine. Primary aromatic amines are commonly prepared by nitrating an aromatic ring, then reducing the nitro group to an amino ($-NH_2$) group. In effect, by forming and diazotizing an amine, an activated aromatic position can be converted into a wide variety of functional groups. For example, toluene might be converted to a variety of substituted derivatives by using this procedure:



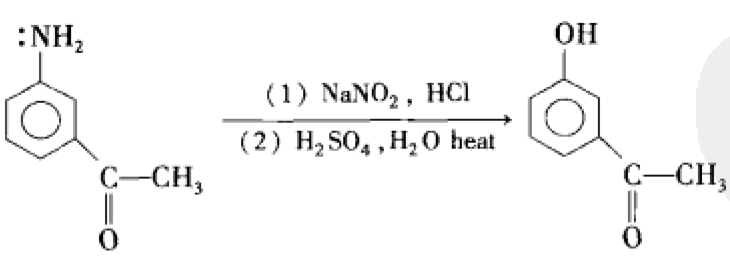
The following flowchart shows some of the functional groups that can be introduced via arenediazonium salts:

	Reagent		Products
$Ar-\overset{+}{N}\equiv N-$	H_3O^+	Ar—OH	phenols
	CuCl(Br)	Ar—Cl(Br)	aryl halides
	CuCN	Ar—C≡N	benzonitriles
	HBF_4(KI)	Ar—F(I)	aryl halides
	H_3PO_2	Ar—H	(deamination)
	H—Ar′	Ar—N=N—Ar′	azo dyes（偶氮染料）

Replacement of the Diazonium Group by Hydroxide: Hydrolysis Hydrolysis takes place when a solution of an arenediazonium salt is strongly acidified (usually by adding H_2SO_4) and warmed. The hydroxyl group of water replaces N_2, forming a phenol. This is a useful laboratory synthesis of phenols because (unlike nucleophilic aromatic substitution) it does not require strong electron-withdrawing substituents or powerful bases and nucleophiles.

$$Ar-\overset{+}{N}\equiv N \quad Cl^- \xrightarrow[H_2O]{H_2SO_4,\ heat} Ar-OH + N_2\uparrow + H^+$$

Example



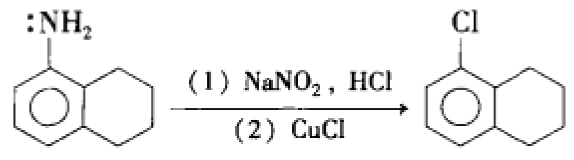
(75%)

Replacement of the Diazonium Group by Chloride, Bromide, and Cyanide: The Sandmeyer Reaction Copper (I) salts (cuprous salts) have a special affinity for diazonium salts. Cuprous chloride, cuprous bromide, and cuprous cyanide react with arenediazonium salts to give aryl chlorides, aryl bromides, and aryl cyanides. It is often necessary to heat the reaction mixture to drive these reactions to completion. The use of cuprous salts to replace arenediazonium groups is called the **Sandmeyer reaction.** The Sandmeyer reaction (using cuprous cyanide) is an excellent method for attaching another carbon substituent to an aromatic ring.

The Sandmeyer reaction

$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N\quad Cl^- \xrightarrow[(X = Cl,\ Br,\ C{\equiv}N)]{CuX} Ar{-}X + N_2\uparrow}$$

Examples



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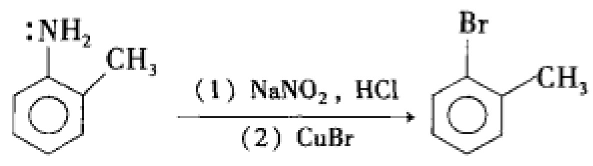

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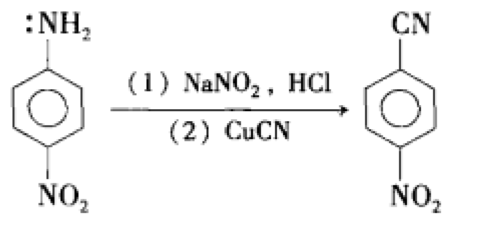


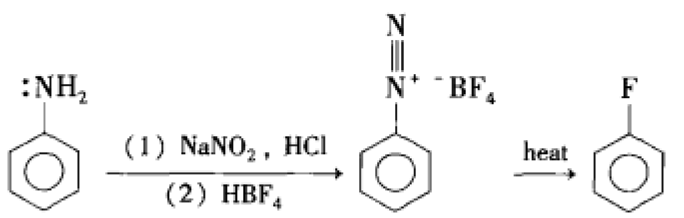
(70%)

Replacement of the Diazonium Group by Fluoride and Iodide When an arenediazonium salt is treated with fluoroboric acid (HBF_4), the diazonium fluoroborate precipitates out of solution. If this precipitated salt is filtered and then heated, it decomposes to give the aryl fluoride. Although this reaction requires the isolation and heating of a potentially explosive diazonium salt, it may be carried out safely if it is done carefully with the proper equipment. There are few other methods for making aryl fluorides.

$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N\quad Cl^- \xrightarrow{HBF_4} \underset{\text{diazonium fluoroborate}}{Ar{-}\overset{+}{N}{\equiv}N\ {}^-BF_4} \xrightarrow{heat} Ar{-}F + N_2\uparrow + BF_3}$$

（氟硼酸重氮盐）

Example

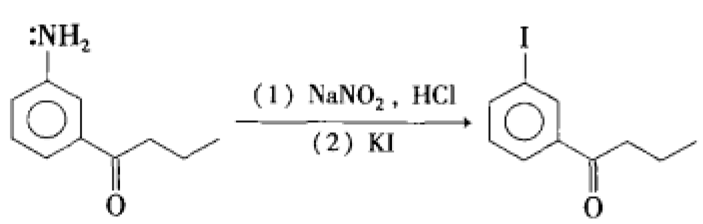


(50%)

Aryl iodides are formed by treating arenediazonium salts with potassium iodide. This is one of the best methods for making iodobenzene derivatives.

$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N\quad Cl^- \xrightarrow{KI} Ar{-}I + N_2\uparrow}$$

Example



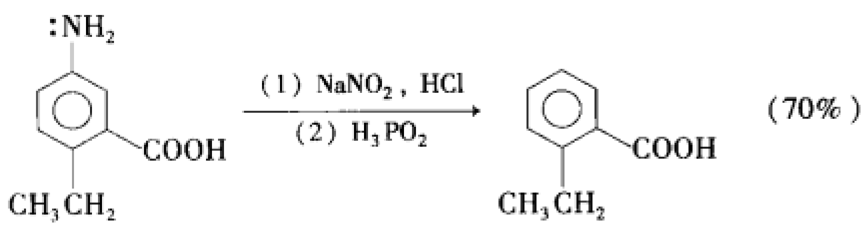
(75%)

Reduction of the Diazonium Group to Hydrogen: Deamination of Anilines Hypophosphorus acid

(H_3PO_2) reacts with arenediazonium salts, replacing the diazonium group with a hydrogen. In effect, this is a reduction of the arenediazonium ion.

$$Ar—\overset{+}{N}≡N \quad Cl^- \xrightarrow{H_3PO_2} Ar—H + N_2\uparrow$$

Example



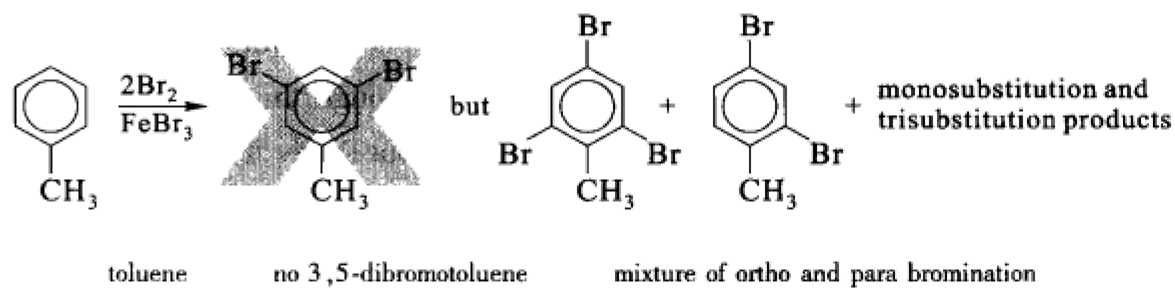
This reaction is sometimes used to remove an amino group that was added to activate the ring.

SOLVED PROBLEM 20-2

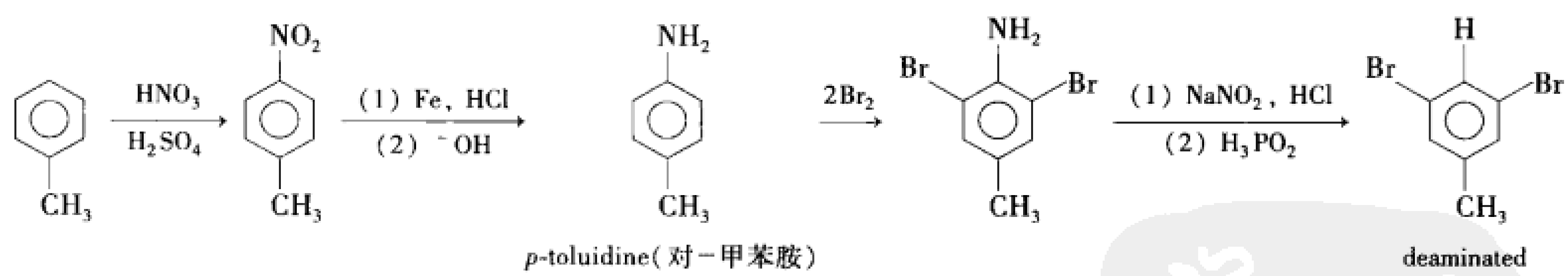
Show how you would convert toluene to 3,5-dibromotoluene in good yield.

SOLUTION

Direct bromination of toluene cannot give 3,5-dibromotoluene because the methyl group activates the ortho and para positions.



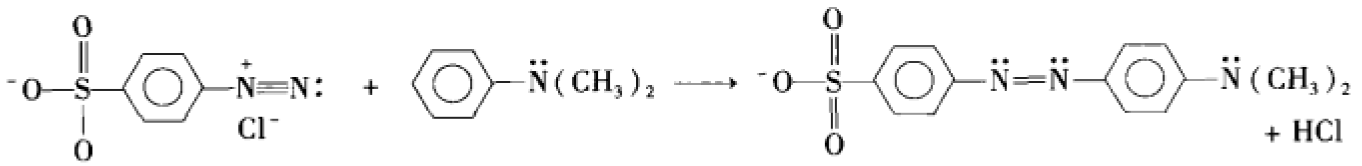
Starting with *p*-toluidine (*p*-methylaniline), however, the strongly activating amino group directs bromination to its ortho positions. Removal of the amino group (deamination) gives the desired product.



Diazonium Salts as Electrophiles: Diazo Coupling Arenediazonium ions act as weak electrophiles in electrophilic aromatic substitutions. The products have the structure Ar—N=N—Ar, containing the —N=N— **azo** linkage. For this reason, the products are called azo compounds, and the reaction is called **diazo coupling.** Because they are weak electrophiles, diazonium salts react only with strongly activated rings (such as derivatives of aniline and phenol).

$$\underset{\text{diazonium ion (重氮离子)}}{Ar—\overset{+}{N}≡N} + \underset{\text{(activated)}}{H—Ar'} \longrightarrow \underset{\text{an azo compound (偶氮化合物)}}{Ar—N=N—Ar'} + H^+$$

Example

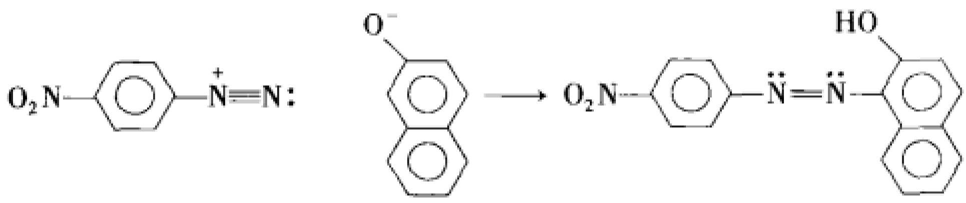


methyl orange (an indicator)
(甲基橙)

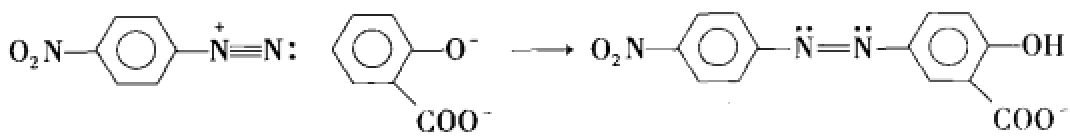
PROBLEM 20−12

Propose a mechanism for the synthesis of methyl orange.

Azo compounds bring two substituted aromatic rings into conjugation with an azo group, which is a strong chromophore. Therefore, most azo compounds are strongly colored, and they make excellent dyes, known as *azo dyes*. The diazo coupling syntheses of some common azo dyes follow.



para red (对位红)

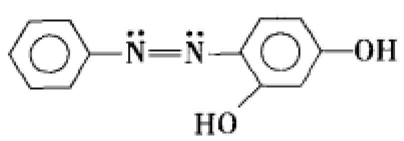


alizarin yellow

Diazo coupling often takes place in basic solutions because deprotonation of the phenolic—OH groups and the sulfonic acid and carboxylic acid groups helps to activate the aromatic rings toward electrophilic aromatic substitution. Many of the common azo dyes have one or more sulfonate ($—SO_3^-$) or carboxylate ($—COO^-$) groups on the molecule to promote solubility in water and to help bind the dye to the polar surfaces of common fibers such as cotton and wool.

PROBLEM 20−13

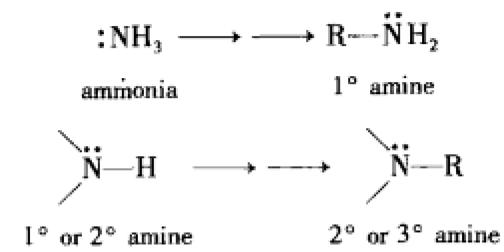
Show how you would convert aniline to the following compounds.

(**a**) fluorobenzene (**b**) chlorobenzene (**c**) 1,3,5-trimethylbenzene
(**d**) bromobenzene (**e**) iodobenzene (**f**) benzonitrile
(**g**) phenol (**h**)  (use aniline and resorcinol)

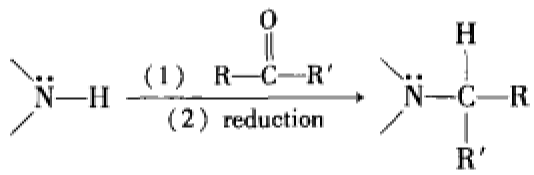
20−17 Synthesis of Amines by Reductive Amination

Many methods are available for making amines. Most of these methods derive from the reactions of amines covered in the preceding sections. The most common amine syntheses start with ammonia or an amine and add an-

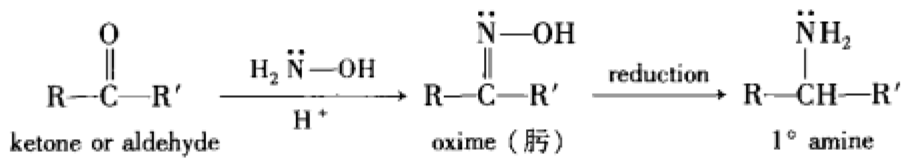
other alkyl group. Such a process converts ammonia to a primary amine, or a primary amine to a secondary amine, or a secondary amine to a tertiary amine.



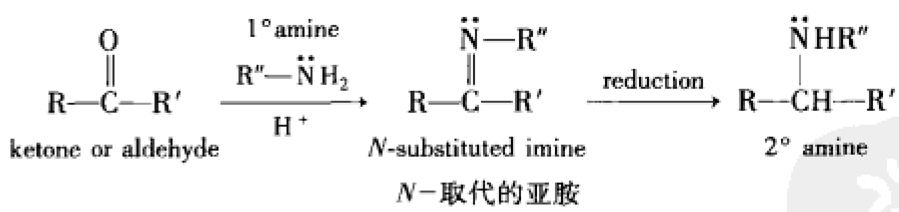
Reductive amination is the most general amine synthesis, capable of adding a primary or secondary alkyl group to an amine. Reductive amination is a two-step procedure. First we form an imine or oxime derivative of a ketone or aldehyde, and then reduce it to the amine. In effect, reductive amination adds one alkyl group to the nitrogen atom. The product can be a primary, secondary, or tertiary amine, depending on whether the starting amine had zero, one, or two alkyl groups.



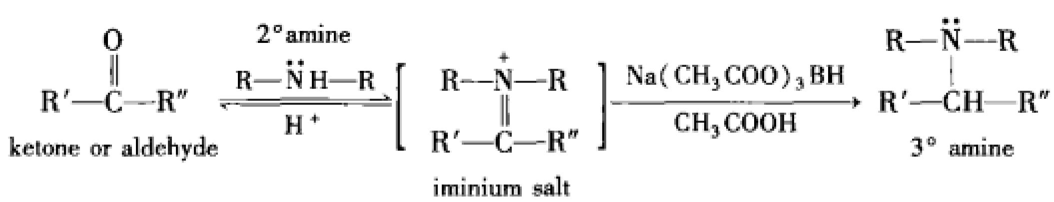
Primary Amines Primary amines result from condensation of hydroxylamine (zero alkyl groups) with a ketone or an aldehyde, followed by reduction of the oxime. Hydroxylamine is used in place of ammonia because most oximes are stable, easily isolated compounds. The oxime is reduced using catalytic reduction, lithium aluminum hydride, or zinc and HCl.



Secondary Amines Condensation of a primary amine with a ketone or aldehyde forms an *N*-substituted imine (a Schiff base). Reduction of the imine gives a secondary amine.



Tertiary Amines Condensation of a secondary amine with a ketone or aldehyde gives an iminium salt. Iminium salts are frequently unstable, so they are rarely isolated. A reducing agent in the solution reduces the iminium salt to a tertiary amine. The reducing agent must reduce the iminium salt, but it must not reduce the carbonyl group of the ketone or aldehyde. Sodium triacetoxyborohydride [$Na(CH_3COO)_3BH$ or $Na(AcO)_3BH$] is less reactive than sodium borohydride, and it does not reduce the carbonyl group. Sodium triacetoxyborohydride has largely replaced an older reagent, sodium cyanoborohydride ($NaBH_3CN$), which is more toxic and not as effective.



PROBLEM 20-14

Show how to synthesize the following amines from the indicated starting materials by reductive amination.

(a) benzylmethylamine from benzaldehyde

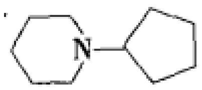
(b) $Ph{-}CH_2{-}CH(\ddot{N}H_2){-}CH_3$ from $Ph{-}CH_2{-}C(=O){-}CH_3$

(±)-amphetamine 1-phenyl-2-propanone

(c) *N*-benzylpiperidine from piperidine

(d) *N*-cyclohexylaniline from cyclohexanone

(e) cyclohexylamine from cyclohexanone

(f)  from compounds containing no more than five carbon atoms

20-18 Synthesis of Amines by Acylation-Reduction

The second general synthesis of amines is **acylation-reduction.** Like reductive amination, acylation-reduction adds one alkyl group to the nitrogen atom of the starting amine. Acylation of the starting amine by an acid chloride gives an amide, which is much less nucleophilic and unlikely to overacylate. Reduction of the amide by lithium aluminum hydride ($LiAlH_4$) gives the corresponding amine.

$$\underset{\text{amine}}{R{-}\ddot{N}H_2} + \underset{\text{acid chloride}}{Cl{-}\overset{O}{\overset{\|}{C}}{-}R'} \xrightarrow[\text{pyridine or NaOH}]{\text{acylation}} \underset{\text{amide}}{R{-}\ddot{N}H{-}\overset{O}{\overset{\|}{C}}{-}R'} \xrightarrow[(2)\ H_2O]{\text{reduction}\ (1)\ LiAlH_4} \underset{\text{alkylated amine}}{R{-}\ddot{N}H{-}CH_2{-}R'}$$

Acylation-reduction converts ammonia to a primary amine, a primary amine to a secondary amine, or a secondary amine to a tertiary amine. These reactions are quite general, with one restriction: The added alkyl group is always 1° because the carbon bonded to nitrogen is derived from the carbonyl group of the amide, reduced to a methylene ($-CH_2-$) group.

Primary amines

$$\underset{\text{acid chloride}}{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + \underset{\text{ammonia}}{\ddot{N}H_3} \longrightarrow \underset{1^\circ\ \text{amide}}{R{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}H_2} \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4} \underset{1^\circ\ \text{amine}}{R{-}CH_2{-}\ddot{N}H_2}$$

Secondary amines

$$\underset{\text{acid chloride}}{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + \underset{\text{primary amine}}{R'{-}\ddot{N}H_2} \longrightarrow \underset{N\text{-substituted amide}}{R{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}H{-}R'} \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4} \underset{2^\circ\ \text{amine}}{R{-}CH_2{-}\ddot{N}H{-}R'}$$

Tertiary amines

$$\underset{\text{acid chloride}}{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + \underset{\text{secondary amine}}{R'_2\ddot{N}H} \longrightarrow \underset{N,N\text{-disubstituted amide}}{R{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}R'_2} \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4} \underset{3^\circ\ \text{amine}}{R{-}CH_2{-}\ddot{N}R'_2}$$

PROBLEM 20-15

Show how to synthesize the following amines from the indicated starting materials by acylation-reduction

(a) *N*-propylpiperidine from piperidine

(b) *N*-benzylaniline from aniline

20-19 Syntheses Limited to Primary Amines

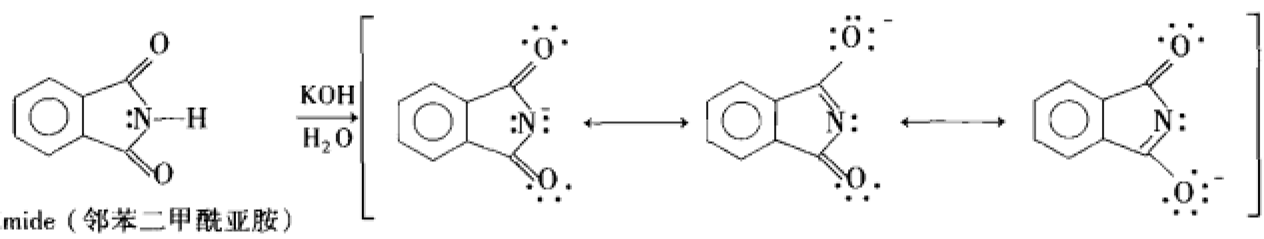
Primary amines are the most common class of amines, and they are also used as starting materials for synthesis of secondary and tertiary amines. Many methods have been developed for making primary amines, ranging from simple alkylation of ammonia to sophisticated multistep syntheses. We will consider some of the more common syntheses.

20-19A Direct Alkylation and Gabriel Synthesis

The S_N2 reaction of amines with alkyl halides is complicated by a tendency for over-alkylation to form a mixture of monoalkylated and polyalkylated products. Simple primary amines can be synthesized, however, by adding a halide or tosylate (must be a good S_N2 substrate) to a large excess of ammonia. Because there is a large excess of ammonia present, the probability that a molecule of the halide will alkylate ammonia is much larger than the probability that it will overalkylate the amine product.

$$R{-}CH_2{-}X + \text{excess } NH_3 \longrightarrow R{-}CH_2{-}NH_2 + NH_4^+X^-$$

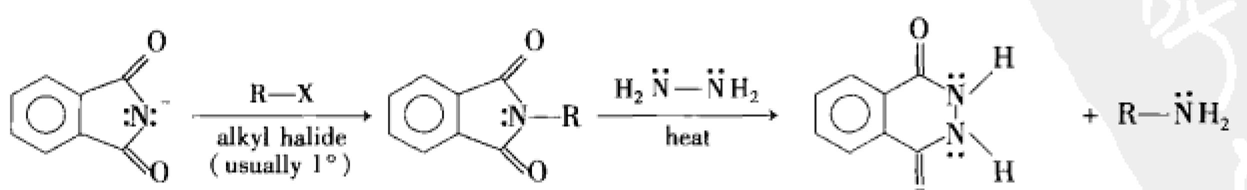
In 1887, Siegmund Gabriel (at the University of Berlin) developed the **Gabriel amine synthesis** for making primary amines without danger of overalkylation. He used the phthalimide anion as a protected form of ammonia that cannot alkylate more than once. Phthalimide has one acidic N—H proton (pK_a 8.3) that is abstracted by potassium hydroxide to give the phthalimide anion.



phthalimide (邻苯二甲酰亚胺)

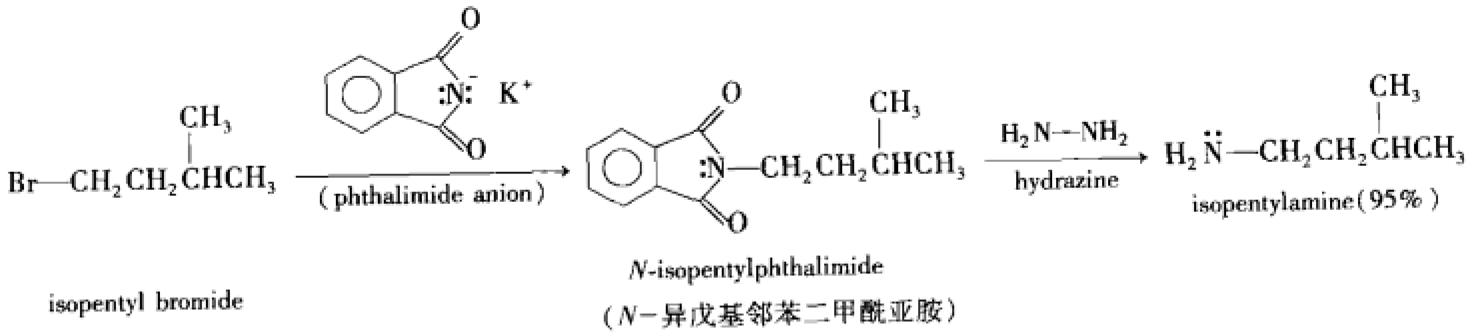
resonance-stabilized phthalimide anion
(共振-稳定的邻苯二甲酰亚胺负离子)

The phthalimide anion is a strong nucleophile, displacing a halide or tosylate ion from a good S_N2 substrate. Heating the *N*-alkyl phthalimide with hydrazine displaces the primary amine, giving the very stable hydrazide of phthalimide.



phthalimide anion　　*N*-alkyl phthalimide　　phthalimide hydrazide (邻苯二甲酰肼)　　primary amine

Example



PROBLEM 20-16

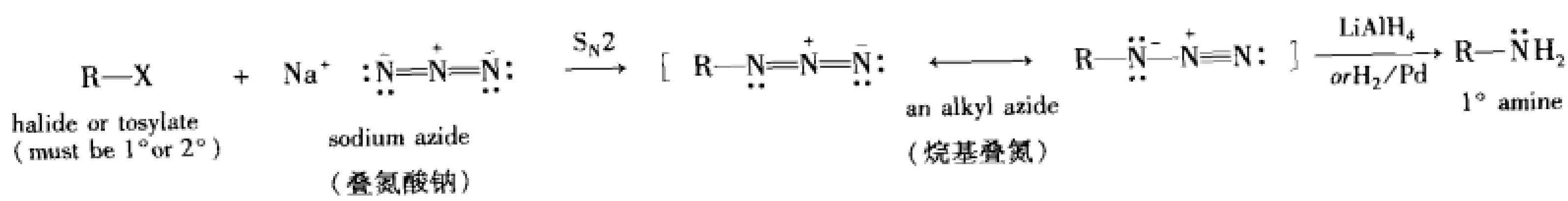
Show how Gabriel syntheses might be used to prepare the following amines.

(a) benzylamine (b) 1-hexanamine (c) γ-aminobutyric acid

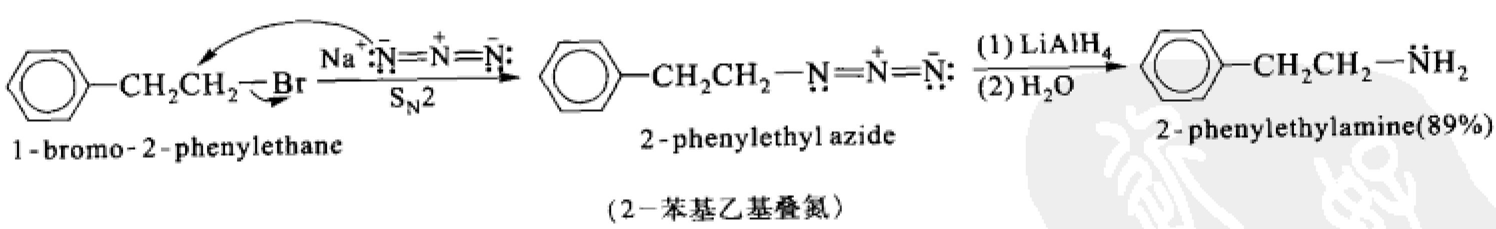
20-19B Reduction of Azides and Nitriles

Just as Gabriel used the anion of phthalimide to put the nitrogen atom into a primary amine, we can use other nucleophiles as well. We need a good nucleophile that can alkylate only once and that is easily converted to an amino group. Two good nucleophiles for introducing a nitrogen atom are the azide ion and the cyanide ion. Azide ion introduces (after reduction) an—NH_2 group, and cyanide ion introduces a —CH_2—NH_2 group.

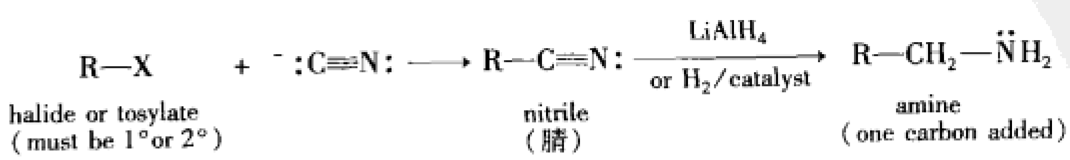
Formation and Reduction of Azides **Azide** ion ($^-N_3$) is an excellent nucleophile that displaces leaving groups from unhindered primary and secondary alkyl halides and tosylates. The products are alkyl azides (RN_3), which have no tendency to react further. Azides are easily reduced to primary amines, either by $LiAlH_4$ or by catalytic hydrogenation. Alkyl azides can be explosive, so they are reduced without purification.



Examples



Formation and Reduction of Nitriles Like the azide ion, cyanide ion ($^-$:C≡N:) is a good S_N2 nucleophile; it displaces leaving groups from unhindered primary and secondary alkyl halides and tosylates. The product is a **nitrile** (R—C≡N), which has no tendency to react further. Nitriles are reduced to primary amines by lithium aluminum hydride or by catalytic hydrogenation.



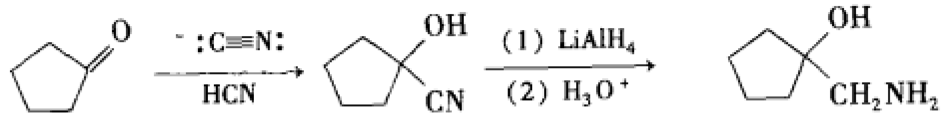
Example

$$CH_3CH_2CH_2Br \xrightarrow{K^+\,^-:C{\equiv}N:} CH_3CH_2CH_2{-}C{\equiv}N: \xrightarrow[(2)\,H_2O]{(1)\,LiAlH_4} CH_3CH_2CH_2{-}CH_2{-}\ddot{N}H_2$$

1-bromopropane — butanenitrile (丁腈) — 1-butanamine(70%)

When the cyano (—C≡N) group is added and reduced, the resulting amine has an additional carbon atom. In effect, the cyanide substitution-reduction process is like adding $—CH_2—NH_2$.

We have seen that cyanide ion adds to ketones and aldehydes to form cyanohydrins. Reduction of the —C≡N group of the cyanohydrin provides a way to synthesize β-hydroxy amines.



cyclopentanone — cyclopentanone cyanohydrin — 1-(methylamino) cyclopentanol

PROBLEM 20-17

Show how you would accomplish the following synthetic conversions.

(**a**) benzyl bromide → benzylamine

(**b**) 1-bromo-2-phenylethane → 3-phenylpropanamine

(**c**) pentanoic acid → 1-pentanamine

(**d**) pentanoic acid → 1-hexanamine

(**e**) (*R*)-2-bromobutane → (*S*)-2-butanamine

(**f**) (*R*)-2-bromobutane → (*S*)-2-methyl-1-butanamine

(**g**) 2-hexanone → 1-amino-2-methyl-2-hexanol

20-19C Reduction of Nitro Compounds

Both aromatic and aliphatic nitro groups are easily reduced to amino groups. The most common methods are catalytic hydrogenation and acidic reduction by an active metal.

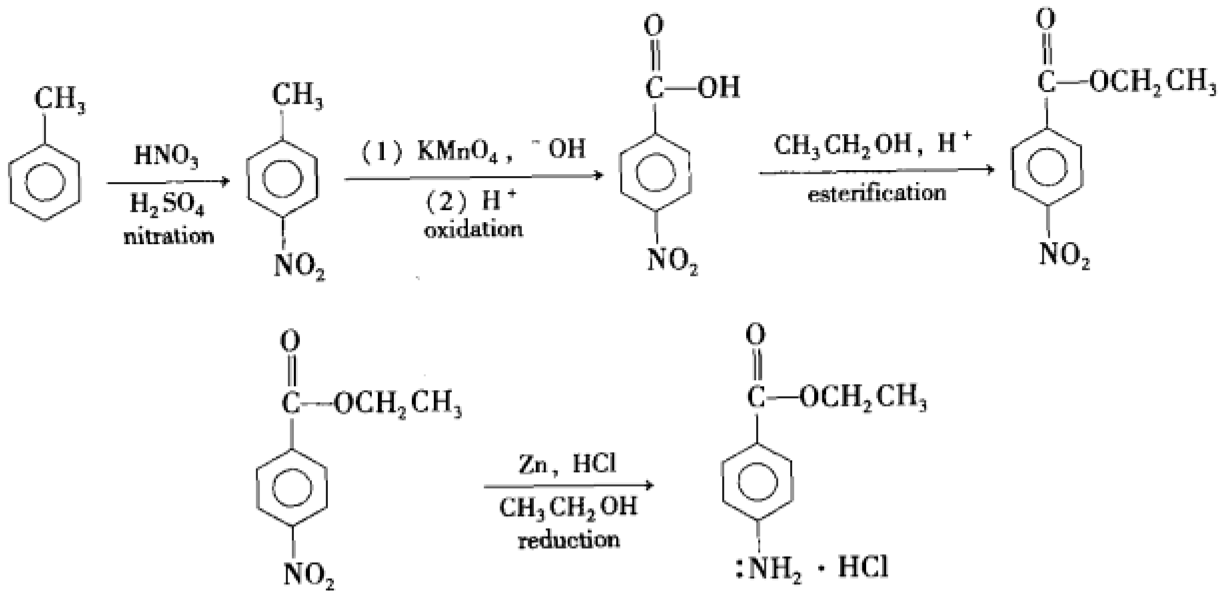
$$R{-}NO_2 \xrightarrow[\text{or active metal and } H^+]{H_2/\text{catalyst}} R{-}NH_2$$

catalyst = Ni, Pd, or Pt
active metal = Fe, Zn, or Sn

The most common reason for reducing aromatic nitro compounds is to make substituted anilines. Much of this chemistry was developed by the dye industry, which uses aniline derivatives for azo coupling reactions to make aniline dyes. Nitration of an aromatic ring (by electrophilic aromatic substitution) gives a nitro compound, which is reduced to the aromatic amine.

$$Ar{-}H \xrightarrow{HNO_3,\ H_2SO_4} Ar{-}NO_2 \xrightarrow{\text{reduction}} Ar{-}NH_2$$

For example, nitration followed by reduction is used in the synthesis of benzocaine (a topical anesthetic), shown below. Notice that the stable nitro group is retained through an oxidation and esterification. The final step reduces the nitro group to the relatively sensitive amine (which could not survive the oxidation step).



benzocaine·HCl

（对氨基苯甲酸乙酯盐酸盐）

PROBLEM 20-18

Show how you would prepare the following aromatic amines by aromatic nitration, followed by reduction. You may use benzene and toluene as your aromatic starting materials.

(a) aniline (b) *p*-bromoaniline

(c) *m*-bromoaniline (d) *m*-aminobenzoic acid

20-19D The Hofmann Rearrangement of Amides

In the presence of a strong base, primary amides react with chlorine or bromine to form shortened amines with loss of the carbonyl carbon atom. This reaction, called the **Hofmann rearrangement**, is used to synthesize primary alkyl and aryl amines.

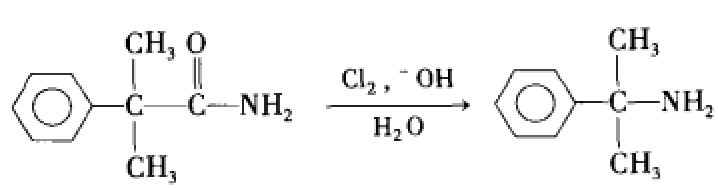
The Hofmann rearrangement

$$\underset{\text{primary amide}}{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\ddot{N}H_2} + \underset{(X_2 = Cl_2 \text{ or } Br_2)}{X_2} + 4NaOH \longrightarrow \underset{\text{amine}}{R{-}\ddot{N}H_2} + 2NaX + Na_2CO_3 + 2H_2O$$

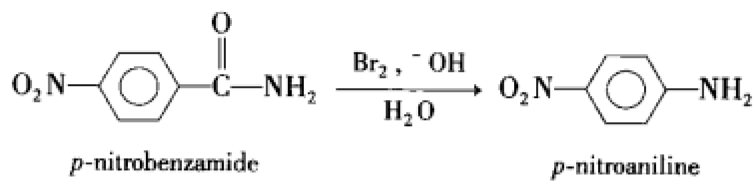
Although we have several other methods for making primary amines, most of them depend on S_N2 displacements, which fail with 3° alkyl groups. The Hofmann rearrangement can produce primary amines with 1°, 2°, or 3° alkyl groups, or aryl amines. The following examples suggest the wide variety of amines that are accessible by the Hofmann rearrangement:

Examples

$$\underset{\text{hexanamide}}{CH_3CH_2CH_2CH_2CH_2{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NH_2} \xrightarrow[H_2O]{Cl_2,\ ^-OH} \underset{\text{1-pentanamine (90\%)}}{CH_3CH_2CH_2CH_2CH_2{-}NH_2}$$



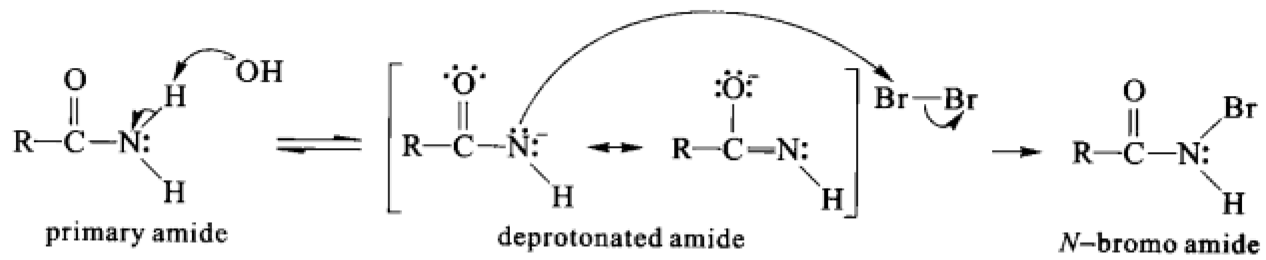
2-methyl-2-phenylpropanamide 2-phenyl-2-propanamine



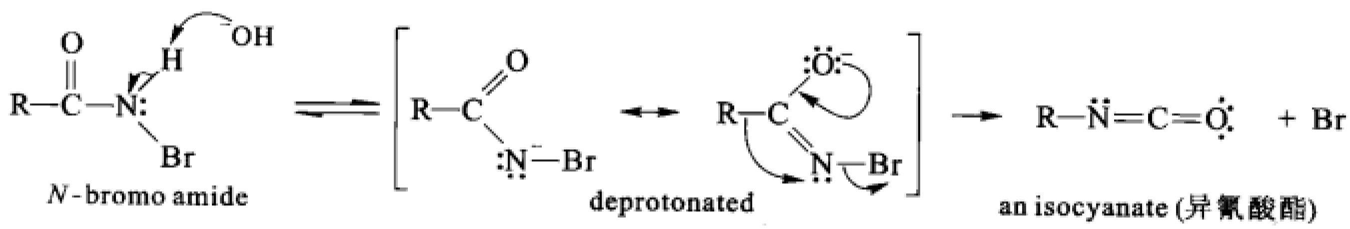
The mechanism of the Hofmann rearrangement is particularly interesting because it involves some intermediates that we have not encountered before. The first step is the replacement of one of the hydrogens on nitrogen by a halogen. This step is possible because the amide N—H protons are slightly acidic, and a strong base deprotonates a small fraction of the amide molecules. The deprononated amide is a strong nucleophile, and it attacks bromine to form the *N*-bromo amide.

MECHANISM 20-5 The Hofmann Rearrangement of Amides

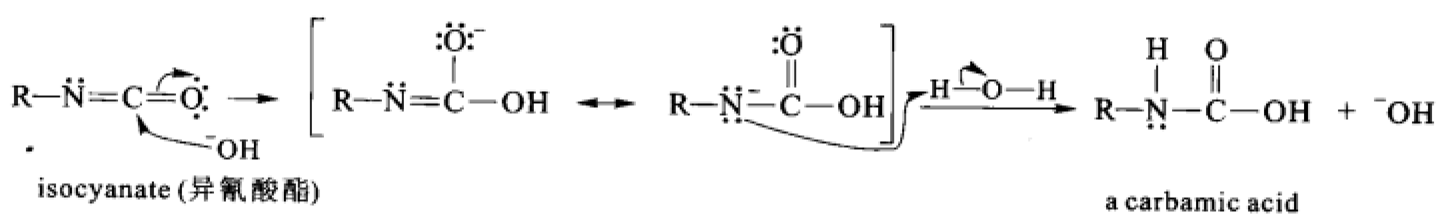
Part 1: Deprotonation of the amide and nucleophilic attack on bromine.



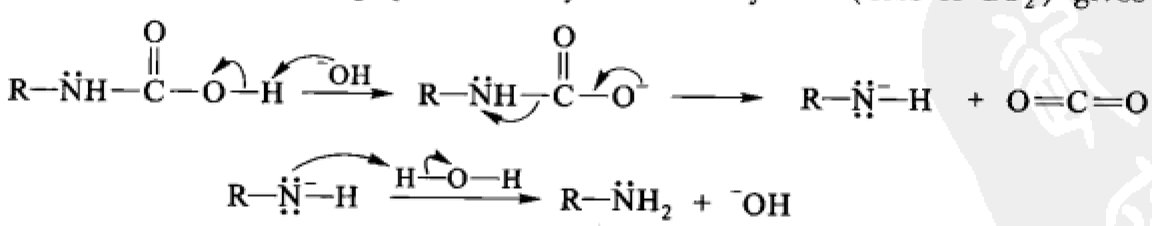
Part 2: *Second deprotonation.* The presence of a leaving group (bromine) allows the alkyl group to migrate and the leaving group to leave.



Part 3: Isocyanates react rapidly with water to give carbamic acids. Hydroxide ion attacks the carbonyl group of the isocyanate.

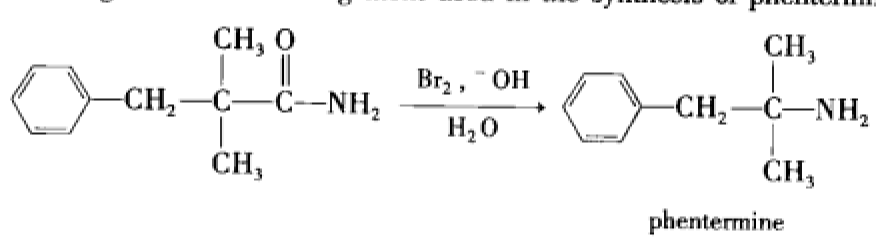


Part 4: Carbamic acids tend to lose CO_2 spontaneously. Decarboxylation (loss of CO_2) gives the amine.



PROBLEM 20-19

Propose a mechanism for the following Hofmann rearrangement used in the synthesis of phentermine, an appetite suppressant.



Summary in Chinese

本 章 概 要

一、胺的结构

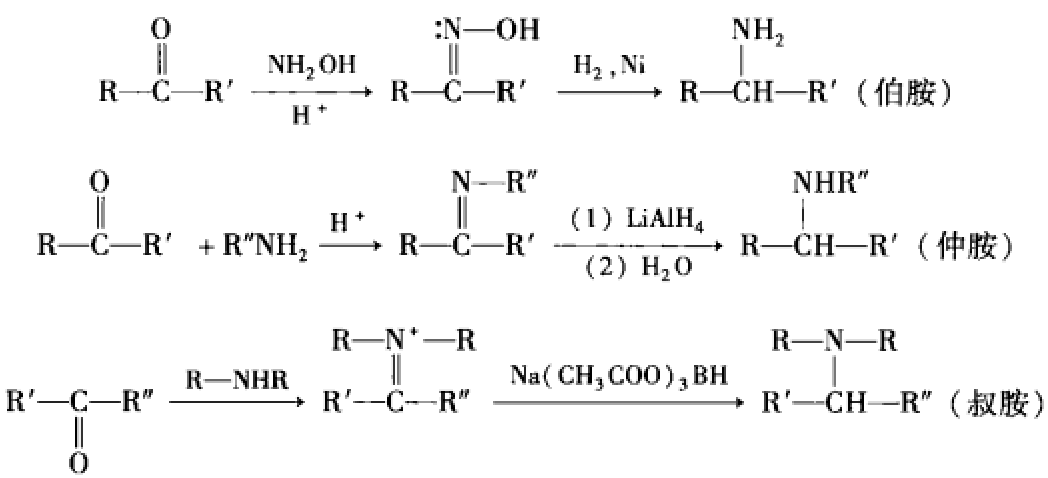
胺的结构与 NH_3 相似，胺分子中氮原子为 sp^3 杂化，具有锥形结构。氮原子以三个 sp^3 杂化轨道分别与其他相连原子形成三个 σ 键，另一个 sp^3 杂化轨道上有一对未成键电子。胺可以根据氮原子上所连烃基的数目不同分为伯、仲、叔胺及季铵盐。

二、胺的物理性质

除叔胺外，伯、仲胺均可形成分子间氢键，又由于氮的电负性不如氧强，胺分子之间的氢键不如醇分子间氢键强，因此，胺的沸点比具有相近相对分子质量的非极性化合物高，而比相对分子质量相似的醇的沸点低。在相对分子质量相同的胺中，其沸点高低顺序为 1°胺 > 2°胺 > 3°胺；伯、仲、叔胺都能与水形成氢键，低碳数的胺均可溶于水。

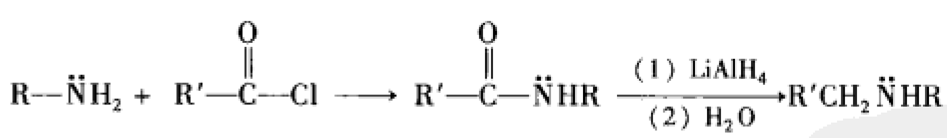
三、胺的合成

1. 还原胺化(reduction amination)：



☆ 可用于制备伯、仲、叔胺。

2. 胺的酰化-还原(acylation-reduction of amines)：



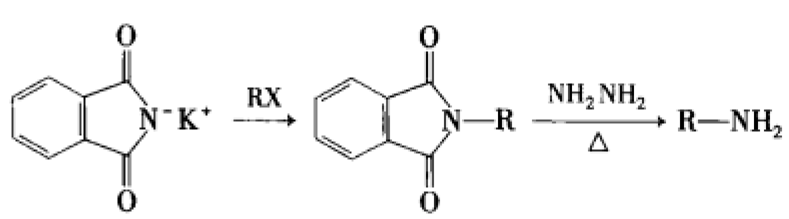
☆ 可用于制备伯、仲、叔胺。

3. 氨的烷基化(alkylation of ammonia)：

$$RCH_2X + 过量\ \ddot{N}H_3 \longrightarrow RCH_2\ddot{N}H_2 + NH_4X$$

☆ 需要用过量的氨以防止生成多烷基化产物。

4. Gabriel 合成(Gabriel synthesis)：



☆ 用于制备伯胺,产率高,纯度好。

5. 叠氮的还原(reduction of azides):

$$R-\ddot{N}=\overset{+}{N}=\ddot{\underset{\cdot\cdot}{N}}^{-}\xrightarrow[\text{或 } H_2, Pd]{LiAlH_4}R-NH_2$$

6. 腈的还原(reduction of nitriles):

$$R-C\equiv N: \xrightarrow[\text{或 } H_2, Pd]{LiAlH_4} RCH_2NH_2$$

☆ 制备同碳数的胺。

7. 硝基化合物的还原(reduction of nitro compounds):

$$R-NO_2 \xrightarrow[\text{或 } Fe, HCl]{H_2, Ni} R-NH_2$$

8. Hofmann 重排 (Hofmann rearrangement):

$$R-\overset{O}{\overset{\|}{C}}-NH_2 + X_2 + 4NaOH \longrightarrow RNH_2 + 2NaX + Na_2CO_3 + 2H_2O$$

$(X = Cl, Br)$

☆ 制备少一个碳原子的胺。

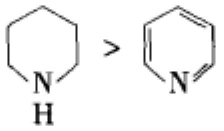
9. 芳香族亲核取代(nucleophilic aromatic substitution):

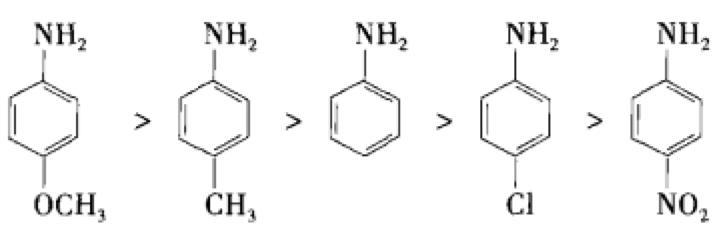
$$R-\ddot{N}H_2 + Ar-X \longrightarrow R-\ddot{N}H-Ar + HX$$

☆ 芳环上连有吸电子基(尤其是在 X 的邻、对位上)有利于反应。

四、胺的化学性质

1. 胺的碱性(basicity of amines):由于胺分子中氮原子有一对未成键的孤对电子,因此胺具有亲核性和碱性。影响化合物碱性的因素很多,如电子效应(共轭效应、诱导效应),空阻效应,溶剂化效应,杂化效应等。下面给出几组化合物的碱性强弱次序:

- 脂肪族胺 > 氨 > 苯胺 > 二苯胺(从电子效应、共轭效应考虑)
- $(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N$(从电子效应、溶剂化效应考虑)
- 脂肪胺 > 吡啶 > 苯胺 > 吡咯(从杂化效应、共轭效应考虑)
-  > $CH_3C\equiv N$

  (从杂化效应考虑)
- 

  (从取代基的电子效应考虑,给电子基使胺碱性增强)

☆ 胺与酸反应生成铵盐。铵盐水溶性好,熔点高,无胺的气味,不易被氧化,加碱又容易变回原来的胺,因此,这一性质常用于胺的分离、提纯、储存及胺类药物应用中。

$$RNH_2(\text{也可以是仲、叔胺}) + HCl \longrightarrow R\overset{+}{N}H_3Cl^- \xrightarrow{NaOH} RNH_2 + NaCl + H_2O$$

2. 胺的烷基化(alkylation of amines):

$$RNH_2 + R'X \longrightarrow R\overset{+}{N}H_2R'\overset{-}{X} \xrightarrow{NaHCO_3} RNHR'$$

$$RNH_2 + \text{过量}\ R'X \xrightarrow{NaHCO_3} R\overset{+}{N}R'_3\overset{-}{X}(\text{季铵盐})$$

☆ 该反应可用于季铵盐的制备。季铵盐常用作相转移催化剂。

3. 胺的酰基化(acylation of amines):

$$RNH_2 + R'\overset{O}{\overset{\|}{C}}—Cl \xrightarrow{\text{吡啶}} R'—\overset{O}{\overset{\|}{C}}—NHR$$

☆ 酰胺在酸或碱的催化下可生成原来的胺,该反应用于氨基的保护。

4. 胺的磺酰化(sulfonylation of amines):

$$\underset{(\text{磺酰氯})}{RNH_2 + R'SO_2Cl} \longrightarrow \underset{(\text{磺酰胺})}{R—\overset{H}{\overset{|}{N}}—\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{S}}}—R'} + HCl$$

☆ 该反应可用于磺胺类药物的合成。

5. 胺的重氮化(diazonium of amines):

(1) 胺的重氮化:

$$RNH_2 \xrightarrow{NaNO_2, HCl} \underset{(\text{烷基重氮盐})}{R\overset{+}{N}\equiv N:Cl^-}$$

$$ArNH_2 \xrightarrow[0\sim5\ ℃]{NaNO_2, HCl} \underset{(\text{芳香重氮盐})}{Ar\overset{+}{N}\equiv N:Cl^-}$$

☆ 烷基重氮盐不稳定,易分解生成 N_2 和碳正离子,碳正离子发生重排、消除等反应生成混合物,没有制备意义。而芳香重氮盐由于苯环的共轭作用较烷基重氮盐稳定,在低温下可以存在,并能发生一系列的反应,合成上有重要意义。

(2) 芳香重氮盐的反应(reaction of arenediazonium salts):

重氮基被取代的反应:

$$Ar\overset{+}{N}\equiv N:Cl^- \xrightarrow[X\ =\ Cl, Br, CN]{CuX} ArX + N_2\uparrow\ (\text{Sandmeyer 反应})$$

$$Ar\overset{+}{N}\equiv N:Cl^- \xrightarrow[H_2O]{H_2SO_4, \triangle} ArOH + N_2\uparrow + HCl$$

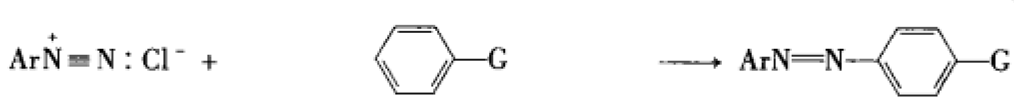
$$Ar\overset{+}{N}\equiv N:Cl^- \xrightarrow[\triangle]{HBF_4} ArF + N_2\uparrow + BF_3$$

$$Ar\overset{+}{N}\equiv N:Cl^- \xrightarrow{KI} ArI + N_2\uparrow + KCl$$

$$Ar\overset{+}{N}\equiv N:Cl^- \xrightarrow{H_3PO_2} ArH + N_2\uparrow$$

☆ 利用这些反应,可在芳环上引入—F、—Cl、—Br、—I、—CN、—OH 等原子或基团,在合成上有重要意义。

重氮偶合反应(diazo coupling reaction):



重氮组分　(G = —OH, —NH_2, —NHR, —NR_2)　(偶氮化合物)

(偶合组分)

☆ 反应机理是苯的亲电取代反应；重氮盐是弱亲电试剂，必须与酚或芳胺电子密度高的化合物反应；重氮组分中芳环上有吸电子基、偶合组分中芳环上有给电子基有利于反应；这一反应用于制备偶氮类染料。

6. Hofmann 消除－季铵碱受热生成烯烃：

$$RCH_2CH_2NH_2 \xrightarrow{3CH_3I} RCH_2CH_2\overset{+}{N}(CH_3)_3I^- \xrightarrow{湿\ Ag_2O} RCH_2CH_2\overset{+}{N}(CH_3)_3OH^-$$

$$R-\underset{H}{\overset{H}{\overset{|}{\underset{|}{C}}}}-\underset{^+N(CH_3)_3}{\underset{|}{CH_2}} + OH^- \xrightarrow{\triangle} RCH=CH_2 + N(CH_3)_3 + H_2O$$

☆ E2 反式消除机理，生成 Hofmann 烯烃，用于推测胺的结构。

7. Cope 消除－叔胺氧化物受热生成烯烃：

$$RCH_2CH_2N(CH_3)_2 \xrightarrow[\text{或 } ArCO_3H]{H_2O_2} RCH_2CH_2\overset{O^-}{\overset{|}{\underset{+}{N}}}(CH_3)_2 \xrightarrow{\triangle} RCH=CH_2 + HO-N(CH_3)_2$$

☆ 该反应是经过环状过渡态的协同反应，顺式消除，生成 Hofmann 烯烃。

五、吡啶的化学性质

吡啶是六元芳香杂环化合物，也是具有碱性的含氮化合物。它具有芳香化合物的一些性质，如亲电取代反应（溴化、硝化等在 3 位上发生），但反应活性不如苯；也具有胺化合物的性质，如碱性、烷基化、酰基化反应（均发生在吡啶氮原子上）。2 位或 4 位卤代吡啶也能发生亲核取代发应。

Essential Problem-Solving Skills in Chapter 20

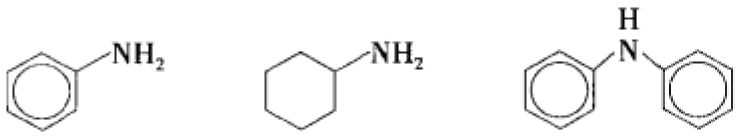
1. Interpret the IR, NMR, and mass spectra of amines, and use the spectral information to determine the structures.
2. Explain how the basicity of amines varies with hybridization and aromaticity.
3. Contrast the physical properties of amines with those of their salts.
4. Predict the products of reactions of amines with the following types of compounds; propose mechanisms where appropriate.
   (a) ketones and aldehydes
   (b) alkyl halides and tosylates
   (c) acid chlorides
   (d) sulfonyl chlorides
   (e) nitrous acid
   (f) oxidizing agents
   (g) arylamines with electrophiles
5. Give examples of the use of arenediazonium salts in diazo coupling reactions and in the synthesis of aryl chlorides, bromides, iodides, fluorides, and nitriles.
6. Illustrate the uses and mechanisms of the Hofmann and Cope eliminations, and predict the major products.
7. Use your knowledge of the mechanisms of amine reactions to propose mechanisms and products of similar reactions you have never seen before.
8. Show how to synthesize amines from other amines, ketones and aldehydes, acid chlorides, nitro compounds, alkyl halides, nitriles, and amides.
9. Use retrosynthetic analysis to propose effective single-step and multistep syntheses of compounds with amines as intermediates or products, protecting the amine as an amide if necessary.

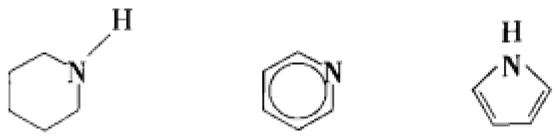
Study Problems

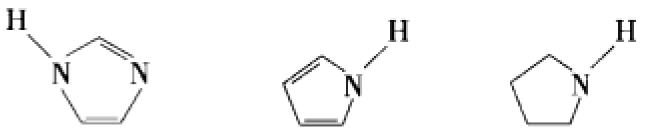
20−20 Define each term and give an example.

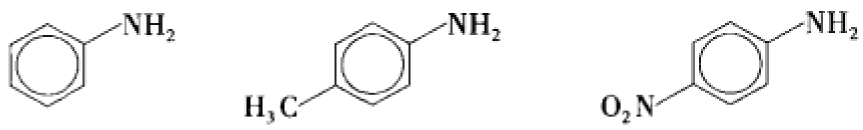
(a) acylation of an amine
(b) a 1° amine
(c) a 2° amine
(d) a 3° amine
(e) an aromatic heterocyclic amine
(f) a tertiary amine oxide
(g) an aliphatic heterocyclic amine
(h) a quaternary ammonium salt
(i) diazotization of an amine
(j) a diazo coupling reaction
(k) exhaustive methylation
(l) a sulfa drug
(m) Gabriel synthesis of an amine
(n) the Hofmann elimination
(o) the Hofmann rearrangement
(p) an *N*-nitrosoamine
(q) reductive amination
(r) the Sandmeyer reaction
(s) a sulfonamide
(t) an azide
(u) a nitrile

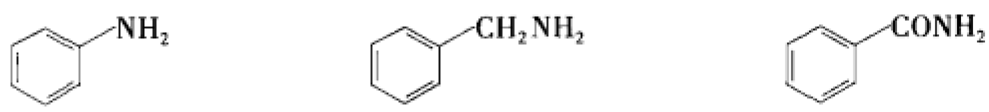
20−21 Rank the amines in each set in order of increasing basicity.

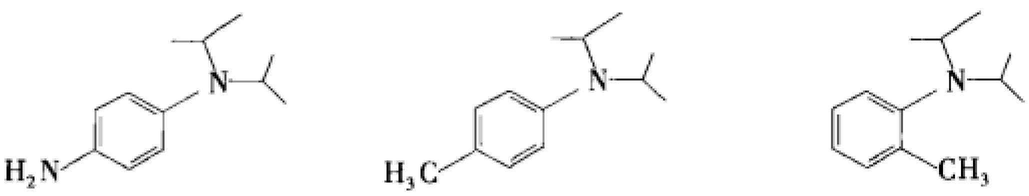
(a) 

(b) 

(c) 

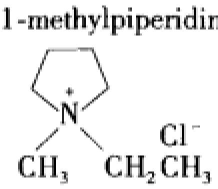
(d) 

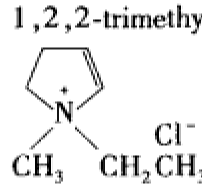
(e) 

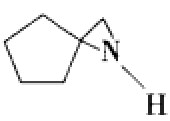
(f) 

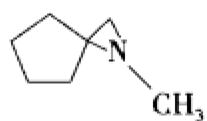
20−22 Which of the following compounds are capable of being resolved into enantiomers?

(a) *N*-ethyl-*N*-methylaniline
(b) 2-methylpiperidine
(c) 1-methylpiperidine
(d) 1,2,2-trimethylaziridine

(e) 

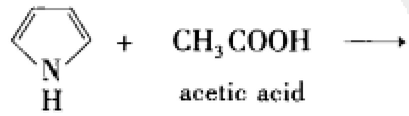
(f) 

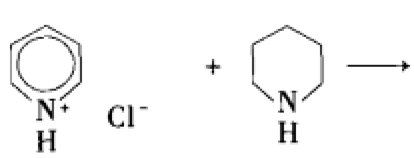
(g) 

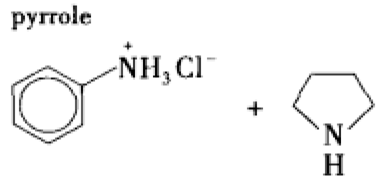
(h) 

20−23 Complete the following proposed acid-base reactions, and predict whether the reactants or products are favored.

(a)
pyridine, acetic acid

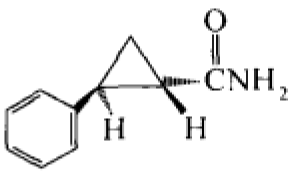
(b) 
pyrrole, acetic acid

(c) 
pyridinium chloride, piperidine

(d) 
anilinium chloride, pyrrolidine

20-24 Predict the organic products formed when the following amides are treated with alkaline bromine water.

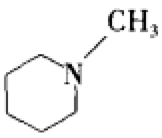
(a) $Ph—CH_2CH_2—C(=O)—NH_2$ (b) $H_2N—C(=O)—(CH_2)_4—C(=O)—NH_2$

(c) 

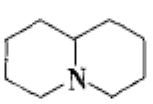
20-25 Predict the products of the following reactions:

(a) excess $NH_3 + Ph—CH_2CH_2CH_2Br \longrightarrow$

(b) 1-bromopentane $\xrightarrow[(2)\ LiAlH_4]{(1)\ NaN_3}$

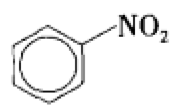
(c)  $+ H_2O_2 \longrightarrow$

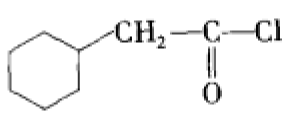
(d) product from part (c) $\xrightarrow{heat}$

(e)  $\xrightarrow[(3)\ heat]{(1)\ excess\ CH_3I\ \ (2)\ Ag_2O}$

(f) product from part (e) $\xrightarrow[(3)\ heat]{(1)\ excess\ CH_3I\ \ (2)\ Ag_2O}$

(g) $+ NaNO_2 + HCl \longrightarrow$

(h)  $\xrightarrow{Zn,\ HCl}$

(i) $CH_3NH_2 +$  $\longrightarrow$

(j) product from part (i) $\xrightarrow{LiAlH_4}$

(k) $CH_3—(CH_2)_3—C(=NCH_3)—CH_2CH_3 \xrightarrow{LiAlH_4}$

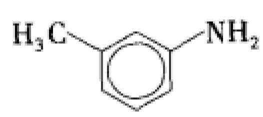
(l) $Ph—CH_2—CH(CN)—CH_3 \xrightarrow{LiAlH_4}$

(m) 2-butanone + diethylamine $\xrightarrow{Na(CH_3COO)_3BH}$

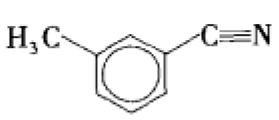
(n) 4-fluoropyridine $\xrightarrow{NaOCH_2CH_3}$

(o) 3-nitroaniline $\xrightarrow[(2)\ H_3PO_2]{(1)\ HCl,\ NaNO_2}$

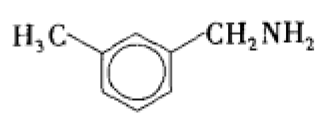
(p) 2-butanone $\xrightarrow[(2)\ LiAlH_4]{(1)\ KCN,\ HCN}$

20-26 Show how *m*-toluidine can be converted to the following compounds,  using any necessary reagents.

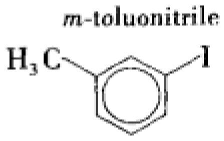
m-toluidine

(a) 

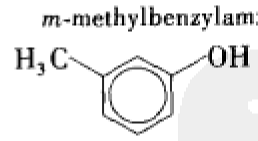
m-toluonitrile

(b) 

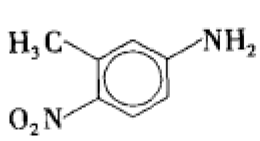
m-methylbenzylamine

(c) 

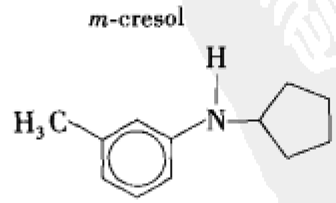
m-iodotoluene

(d) 

m-cresol

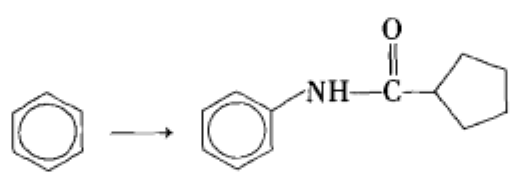
(e) 

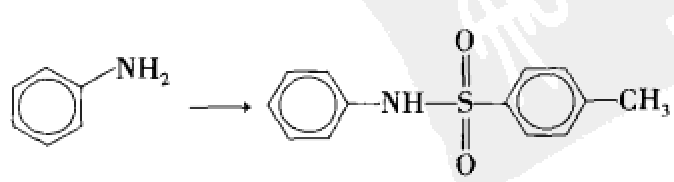
3-methyl-4-nitroaniline

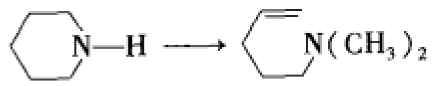
(f) 

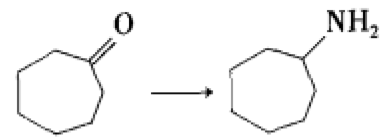
N-cyclopentyl-*m*-toluidine

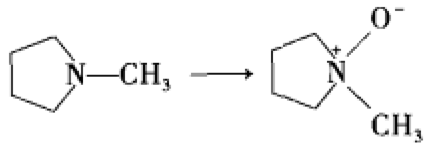
20-27 Using any necessary reagents, show how you would accomplish the following syntheses.

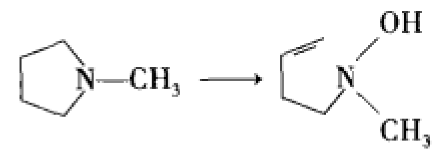
(a) 

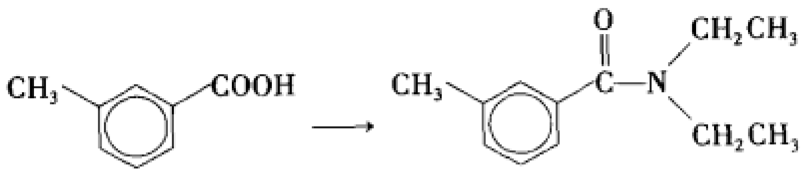
(b) 

(c) 

(d) 

(e) 

(f) 

(g) 

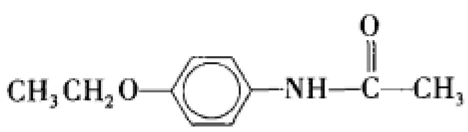
mosquito repellent(驱蚊剂)

20-28 The following drugs are synthesized using the methods in this chapter and in previous chapters. Devise a synthesis for each, starting with any compound containing no more than six carbon atoms.

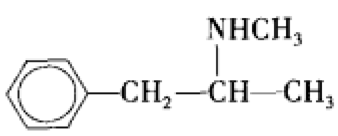
(a) Phenacetin, used with aspirin and caffeine in pain-relief medications.

(b) Methamphetamine, once considered a safe diet pill, but now known to be addictive and destructive to brain tissue.

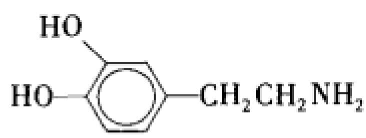
(c) Dopamine, one of the neurotransmitters in the brain. Parkinson's disease is thought to result from a dopamine deficiency.



phenacetin(非那西汀)

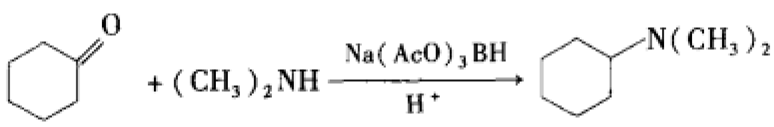


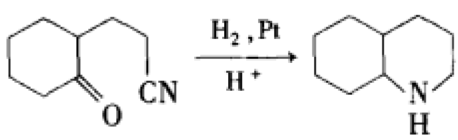
methamphetamine



dopamine(多巴胺)

20-29 Propose mechanisms for the following reactions.

(a) 

(b) 

20-30 The two most general amine syntheses are the reduction of amides and the reductive amination of carbonyl compounds. Show how these techniques can be used to accomplish the following syntheses.

(a) benzoic acid → benzylamine

(b) benzaldehyde → benzylamine

(c) pyrrolidine → *N*-ethylpyrrolidine

(d) cyclohexanone → *N*-cyclohexylpyrrolidine.

(e) HOOC—$(CH_2)_3$—COOH → 1,5-pentanediamine (cadaverine)

20-31 Several additional amine syntheses are effectively limited to making primary amines. The reduction of azides and nitro compounds and the Gabriel synthesis leave the carbon chain unchanged. Formation and reduction of a nitrile adds one carbon atom and the Hofmann rearrangement eliminates one carbon atom. Show how these amine syntheses can be used for the following conversions.

(a) allyl bromide → allylamine

(b) ethylbenzene → *p*-ethylaniline

(c) 3-phenylheptanoic acid → 2-phenyl-1-hexanamine

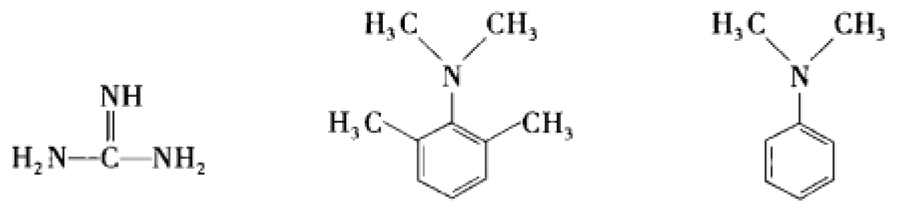
(d) 1-bromo-3-phenylheptane → 3-phenyl-1-heptanamine

(e) 1-bromo-3-phenylheptane → 4-phenyl-1-octanamine

20-32 (a) Guanidine (shown) is about as strong a base as hydroxide ion. Explain why guanidine is a much stronger base than most other amines.

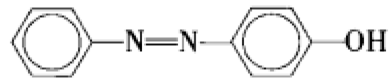
(b) Show why *p*-nitroaniline is a much weaker base (3 pK_b units weater) than aniline.

* (c) Explain why N,N,2,6-tetramethylaniline (shown) is a much stronger base than N,N-dimethylaniline.

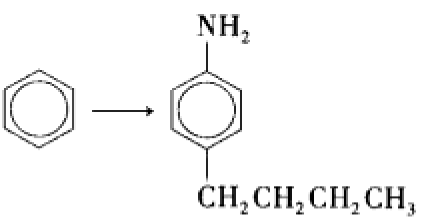


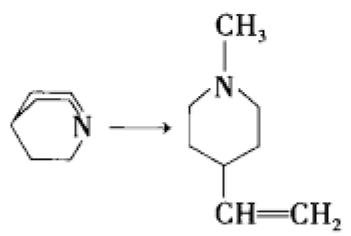
guanidine(胍) N,N,2,6-tetramethylaniline N,N-dimethylaniline

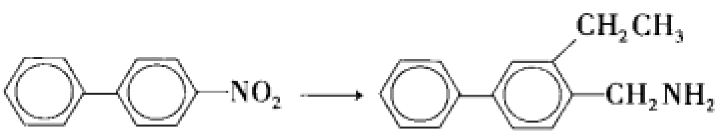
20–33 Show how you would synthesize the following compounds starting with benzene, toluene, and alcohols containing no more than four carbon atoms as your organic starting materials. Assume that para is the major product (and separable from ortho) in ortho, para mixtures.

(a) 1-pentanamine
(b) N-methyl-1-butanamine
(c) N-ethyl-N-propyl-2-butanamine
(d) benzyl-n-propylamine
(e) 
(f) 3-propylaniline
(g) 4-isobutylaniline

20–34 Using any necessary reagents, show how you would accomplish the following multistep syntheses.

(a) 

(b) 

(c) 

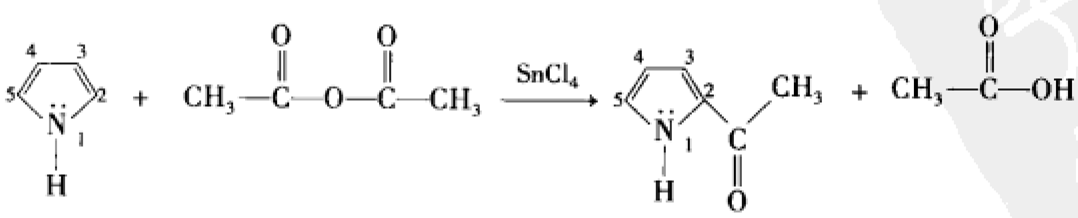
20–35 The alkaloid coniine has been isolated from hemlock and purified. Its molecular formula is $C_8H_{17}N$. Treatment of coniine with excess methyl iodide, followed by silver oxide and heating, gives the pure (S)-enantiomer of N,N-dimethyloct-7-ene-4-amine. Propose a complete structure for coniine, and show how this reaction gives the observed product.

20–36 A chemist is summoned to an abandoned waste-disposal site to determine the contents of a leaking, corroded barrel. The barrel reeks of an overpowering fishy odor. The chemist dons a respirator to approach the barrel and collect a sample, which she takes to her laboratory for analysis.

The mass spectrum shows a molecular ion at m/z 101, and the most abundant fragment is at m/z 86. The IR spectrum shows no absorptions above 3000 cm^{-1}, many absorptions between 2800 and 3000 cm^{-1}, no absorptions between 1500 and 2800 cm^{-1}, and a strong absorption at 1200 cm^{-1}. The proton NMR spectrum shows a triplet ($J = 7$ Hz) at δ1.0 and a quartet($J = 7$ Hz) at δ2.4, with integrals of 17 spaces and 11 spaces, respectively.

(a) Show what structural information is implied by each spectrum, and propose a structure for the unknown toxic waste.
(b) Current EPA regulations prohibit the disposal of liquid wastes because they tend to leak out of their containers. Propose an inexpensive method for converting this waste to a solid, relatively odorless form for reburial.
(c) Suggest how the chemist might remove the fishy smell from her clothing.

20–37 Pyrrole undergoes electrophilic aromatic substitution more readily than benzene, and mild reagents and conditions are sufficient. These reactions normally occur at the 2-position rather than the 3-position, as shown in the following example.

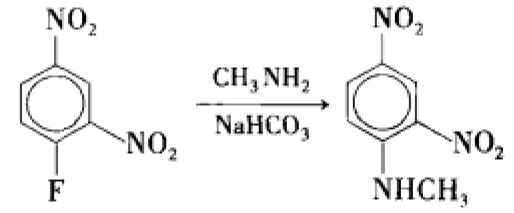


pyrrole acetic anhydride 2-acetylpyrrole

(a) Propose a mechanism for the acetylation of pyrrole just shown. You may begin with pyrrole and the acylium ion, $CH_3—C≡O^+$. Be careful to draw all the resonance structures of the intermediate.

(b) Explain why pyrrole reacts more readily than benzene, and also why substitution occurs primarily at the 2-position rather than the 3-position.

20−38 Section 18−12 showed how nucleophilic aromatic substitution can give aryl amines if there is a strong electron-withdrawing group ortho or para to the site of substitution. Consider the following example.



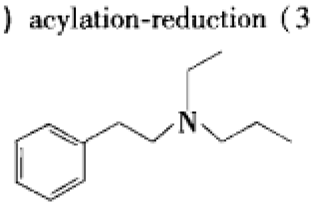
(a) Propose a mechanism for this reaction.

(b) We usually think of fluoride ion as a poor leaving group. Explain why this reaction readily displaces fluoride as the leaving group.

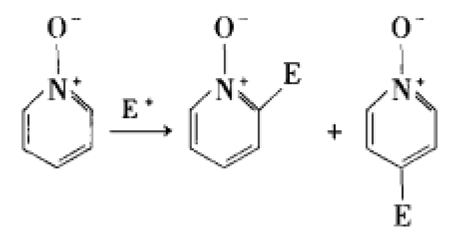
(c) Explain why this reaction stops with the desired product, rather than reacting with another dinitrofluorobenzene.

20−39 Show how you might synthesize the following tertiary amine three different ways, each using a different secondary amine and adding the final substituent by

(a) reductive amination (3 ways). **(b)** acylation-reduction (3 ways).

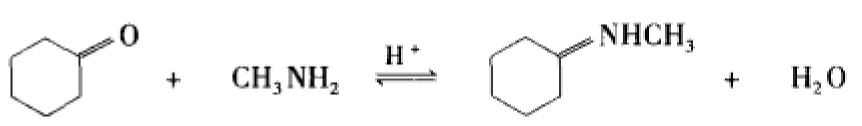


20−40 In Section 20−9B, we saw that pyridine undergoes electrophilic aromatic substitution reluctantly, requiring strong conditions and giving disappointing yields. In contrast, pyridine *N*-oxide undergoes EAS under moderate conditions, giving good yields of substitution on C2 and C4. Explain this surprising difference.



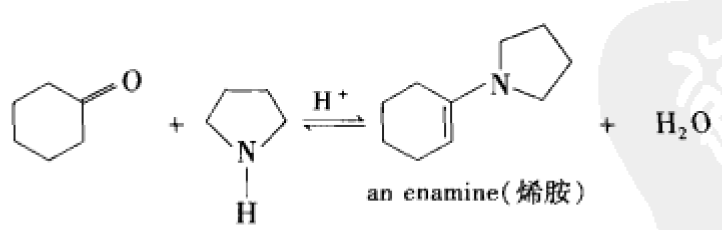
20−41 Ketones and aldehydes react with primary amines to give imines. They react with secondary amines to give *enamines* (vinyl amines).

(a) For review, propose a mechanism for the following formation of an imine.



an imine

(b) Now give a mechanism for a similar reaction that gives an enamine.



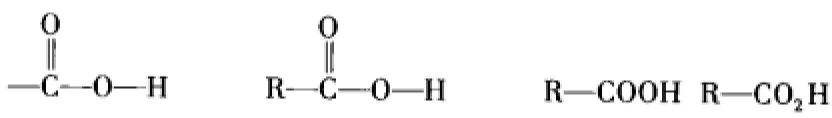
an enamine(烯胺)

(c) Explain why the reaction with the secondary amine gives an enamine rather than an imine.

Chapter 21
Carboxylic Acids

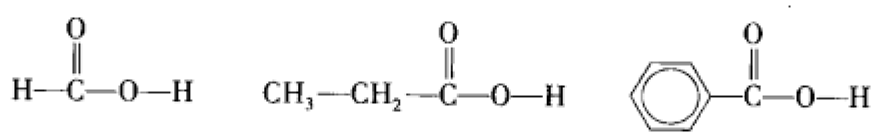
21-1 Introduction

The combination of a **carbo**nyl group and a hydr**oxyl** on the same carbon atom is called a **carboxyl group**. Compounds containing the carboxyl group are distinctly acidic and are called **carboxylic acids**.



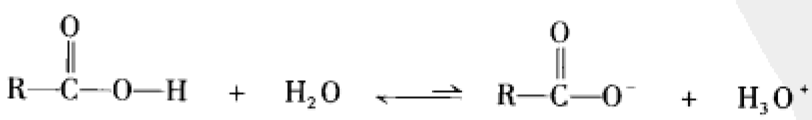
carboxyl group carboxylic acid condensed structures

Carboxylic acids are classified according to the substituent bonded to the carboxyl group. An **aliphatic acid** has an alkyl group bonded to the carboxyl group, and an **aromatic acid** has an aryl group. The simplest acid is *formic acid*, with a proton bonded to the carboxyl group. **Fatty acids** are long-chain aliphatic acids derived from the hydrolysis of fats and oils.



formic acid [甲酸;蚁酸(俗)] propionic acid (an aliphatic acid) stearic acid (硬脂酸) (a fatty acid)

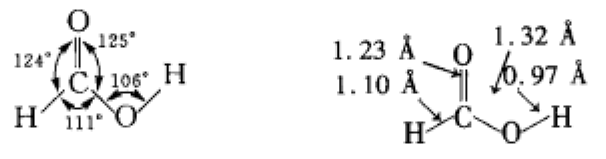
A carboxylic acid donates protons by heterolytic cleavage of the acidic O—H bond to give a proton and a **carboxylate ion**. We consider the ranges of acidity and the factors affecting the acidity of carboxylic acids in Section 21-3.



carboxylic acid carboxylate ion

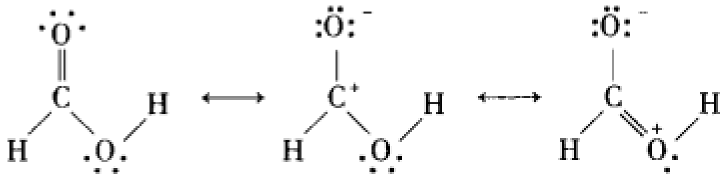
21-2 Structure and Physical Properties of Carboxylic Acids

Structure of the Carboxyl Group The structure of the most stable conformation of formic acid is shown next. The entire molecule is approximately planar. The sp^2 hybrid carbonyl carbon atom is planar, with nearly trigonal bond angles. The O—H bond also lies in this plane, eclipsed with the C=O bond.



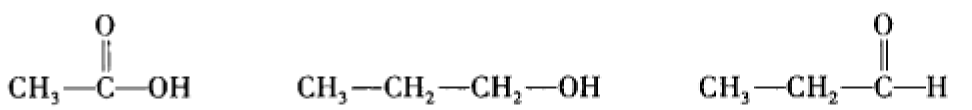
bond angles bond lengths

It seems surprising that an eclipsed conformation is most stable. It appears that one of the unshared electron pairs on the hydroxyl oxygen atom is delocalized into the electrophilic pi system of the carbonyl group. We can draw the following resonance forms to represent this delocalization:



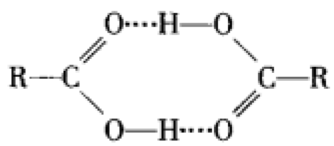
major very minor minor

Boiling Points Carboxylic acids boil at considerably higher temperatures than do alcohols, ketones, or aldehydes of similar molecular weights. For example, acetic acid (MW 60) boils at 118 ℃, 1-propanol (MW 60) boils at 97 ℃, and propionaldehyde (MW 58) boils at 49 ℃.



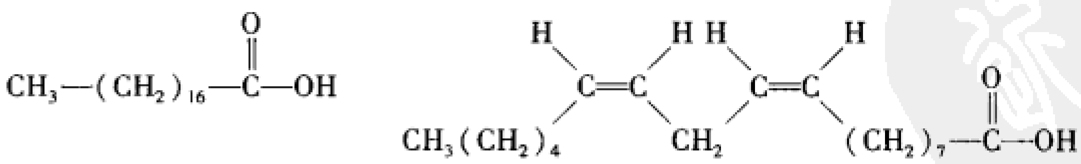
acetic acid, bp 118 ℃ 1-propanol, bp 97 ℃ propionaldehyde, bp 49 ℃

The high boiling points of carboxylic acids result from formation of a stable, hydrogen-bonded dimer. This dimer contains an eight-membered ring joined by two hydrogen bonds, effectively doubling the molecular weight of the molecules leaving the liquid phase.



hydrogen-bonded acid dimer

Melting Points The melting points of some common carboxylic acids are given in Table 21-1. Acids containing more than eight carbon atoms are generally solids, unless they contain double bonds. The presence of double bonds (especially cis double bonds) in a long chain impedes formation of a stable crystal lattice, resulting in a lower melting point. For example, both stearic acid (octadecanoic acid) and linoleic acid (*cis,cis*-9,12-octadecadienoic acid) have 18 carbon atoms, but stearic acid melts at 70 ℃ and linoleic acid melts at -5 ℃.



stearic acid, mp 70 ℃ (硬脂酸) linoleic acid, mp -5 ℃ (亚油酸;罂酸)

TABLE 21-1 Physical Properties of Some Carboxylic Acids

Formula	mp/℃	bp/℃	Solubility /[g·(100 g H_2O)$^{-1}$]	Formula	mp/℃	bp/℃	Solubility /[g·(100 g H_2O)$^{-1}$]
HCOOH	8	101	∞ (miscible)	CH_3CH_2COOH	-21	141	∞
CH_3COOH	17	118	∞	$H_2C{=}CH{-}COOH$	14	141	∞

Continue

Formula	mp/℃	bp/℃	Solubility /[g·(100 g H_2O)$^{-1}$]	Formula	mp/℃	bp/℃	Solubility /[g·(100 g H_2O)$^{-1}$]
$CH_3(CH_2)_2COOH$	-6	163	∞	$CH_3(CH_2)_{14}COOH$	63		i
$(CH_3)_2CHCOOH$	-46	155	23.0	$CH_3(CH_2)_{16}COOH$	72		i
$CH_3—CH═CHCOOH$	71	185	8.6	$CH_3(CH_2)_7CH═CH(CH_2)_7COOH$	16		i
$CH_3(CH_2)_3COOH$	-34	186	3.7	$CH_3(CH_2)_4CH═CHCH_2CH═CH(CH_2)_7COOH$	-5		i
$(CH_3)_2CHCH_2COOH$	-29	177	5.0				
$(CH_3)_3C—COOH$	35	164	2.5				
$CH_3(CH_2)_4COOH$	-4	206	1.0	*c*-$C_6H_{11}COOH$	31	233	0.2
$CH_3(CH_2)_6COOH$	16	240	0.7	C_6H_5COOH	122	249	0.3
$CH_3(CH_2)_8COOH$	31	269	0.2	*o*-$CH_3C_6H_4COOH$	106	259	0.1
$CH_3(CH_2)_{10}COOH$	44		i	*m*-$CH_3C_6H_4COOH$	112	263	0.1
$CH_3(CH_2)_{12}COOH$	54		i	*p*-$CH_3C_6H_4COOH$	180	275	0.03

The melting points of dicarboxylic acids (Table 21-2) are relatively high. With two carboxyl groups per molecule, the forces of hydrogen bonding are particularly strong in diacids; a high temperature is required to break the lattice of hydrogen bonds in the crystal and melt the diacid.

TABLE 21-2 Physical Properties of Dicarboxylic Acids

Formula	mp/℃	Solubility /[g·(100 g H_2O)$^{-1}$]	Formula	mp/℃	Solubility /[g·(100 g H_2O)$^{-1}$]
HOOC—COOH	189	14	*cis*-HOOCCH═CHCOOH	130.5	79
$HOOCCH_2COOH$	136	74	*trans*-HOOCCH═CHCOOH	302	0.7
$HOOC(CH_2)_2COOH$	185	8	1,2-$C_6H_4(COOH)_2$	231	0.7
$HOOC(CH_2)_3COOH$	98	64	1,3-$C_6H_4(COOH)_2$	348	
$HOOC(CH_2)_4COOH$	151	2	1,4-$C_6H_4(COOH)_2$	300 subl.	0.002
$HOOC(CH_2)_5COOH$	106	5			

Solubilities Carboxylic acids form hydrogen bonds with water, and the lowermolecular-weight carboxylic acids (up through 4 carbon atoms) are miscible with water. As the length of the hydrocarbon chain increases, water solubility decreases until acids with more than 10 carbon atoms are essentially insoluble in water. The water solubilities of some simple carboxylic acids and diacids are given in Tables 21-1 and 21-2.

Carboxylic acids are very soluble in alcohols because the acids form hydrogen bonds with alcohols. Also, alcohols are not as polar as water, so the longer-chain acids are more soluble in alcohols than they are in water. Most carboxylic acids are quite soluble in relatively nonpolar solvents such as chloroform because the acid continues to exist in its dimeric form in the nonpolar solvent. Thus, the hydrogen bonds of the cyclic dimer are not disrupted when the acid dissolves in a nonpolar solvent.

21-3 Acidity of Carboxylic Acids

21-3A Measurement of Acidity

A carboxylic acid may dissociate in water to give a proton and a carboxylate ion. The equilibrium constant K_a for this reaction is called the *acid-dissociation constant*. The pK_a of an acid is the negative logarithm of K_a, and we commonly use pK_a as an indication of the relative acidities of different acids (Table 21-3).

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-H \quad + \quad H_2O \quad \rightleftharpoons \quad R-\overset{\overset{\displaystyle O}{\|}}{C}-O^- \quad + \quad H_3O^+$$

$$K_a = \frac{[R-CO_2^-][H_3O^+]}{[R-CO_2H]}$$

$$pK_a = -\lg K_a$$

TABLE 21-3 Values of K_a and pK_a for Carboxylic Acids and Dicarboxylic Acids

Formula	Values			
	Simple carboxylic acids			
	K_a (at 25 ℃)			pK_a
HCOOH	1.77×10^{-4}			3.75
CH_3COOH	1.76×10^{-5}			4.74
CH_3CH_2COOH	1.34×10^{-5}			4.87
$CH_3(CH_2)_2COOH$	1.54×10^{-5}			4.82
$CH_3(CH_2)_3COOH$	1.52×10^{-5}			4.81
$CH_3(CH_2)_4COOH$	1.31×10^{-5}			4.88
$CH_3(CH_2)_6COOH$	1.28×10^{-5}			4.89
$CH_3(CH_2)_8COOH$	1.43×10^{-5}			4.84
C_6H_5COOH	6.46×10^{-5}			4.19
p-$CH_3C_6H_4COOH$	4.33×10^{-5}			4.36
p-ClC_6H_4COOH	1.04×10^{-4}			3.98
p-$NO_2C_6H_4COOH$	3.93×10^{-4}			3.41
	Dicarboxylic acids			
	K_{a1}	pK_{a1}	K_{a2}	pK_{a2}
HOOC—COOH	5.4×10^{-2}	1.27	5.2×10^{-5}	4.28
$HOOCCH_2COOH$	1.4×10^{-3}	2.85	2.0×10^{-6}	5.70
$HOOC(CH_2)_2COOH$	6.4×10^{-5}	4.19	2.3×10^{-6}	5.64
$HOOC(CH_2)_3COOH$	4.5×10^{-5}	4.35	3.8×10^{-6}	5.42
$HOOC(CH_2)_4COOH$	3.7×10^{-5}	4.43	3.9×10^{-6}	5.41
cis-HOOCCH=CHCOOH	1.0×10^{-2}	2.00	5.5×10^{-7}	6.26
trans-HOOCCH=CHCOOH	9.6×10^{-4}	3.02	4.1×10^{-5}	4.39
1,2-$C_6H_4(COOH)_2$	1.1×10^{-3}	2.96	4.0×10^{-6}	5.40
1,3-$C_6H_4(COOH)_2$	2.4×10^{-4}	3.62	2.5×10^{-5}	4.60
1,4-$C_6H_4(COOH)_2$	2.9×10^{-4}	3.54	3.5×10^{-5}	4.46

Values of pK_a are about 5 ($K_a = 10^{-5}$) for simple carboxylic acids. For example, acetic acid has a pK_a of 4.7 ($K_a = 1.8 \times 10^{-5}$). Although carboxylic acids are not as strong as most mineral acids, they are still much

more acidic than other functional groups we have studied. For example, alcohols have pK_a values in the range 16 to 18. Acetic acid ($pK_a = 4.74$) is about 10^{11} times as acidic as the most acidic alcohols! In fact, concentrated acetic acid causes acid burns when it comes into contact with the skin.

Dissociation of either an acid or an alcohol involves breaking an O—H bond, but dissociation of a carboxylic acid gives a carboxylate ion with the negative charge spread out equally over *two* oxygen atoms, compared with just one oxygen in an alkoxide ion (Figure 21-1). The delocalized charge makes the carboxylate ion more stable than the alkoxide ion; therefore, dissociation of a carboxylic acid to a carboxylate ion is less endothermic than dissociation of an alcohol to an alkoxide ion.

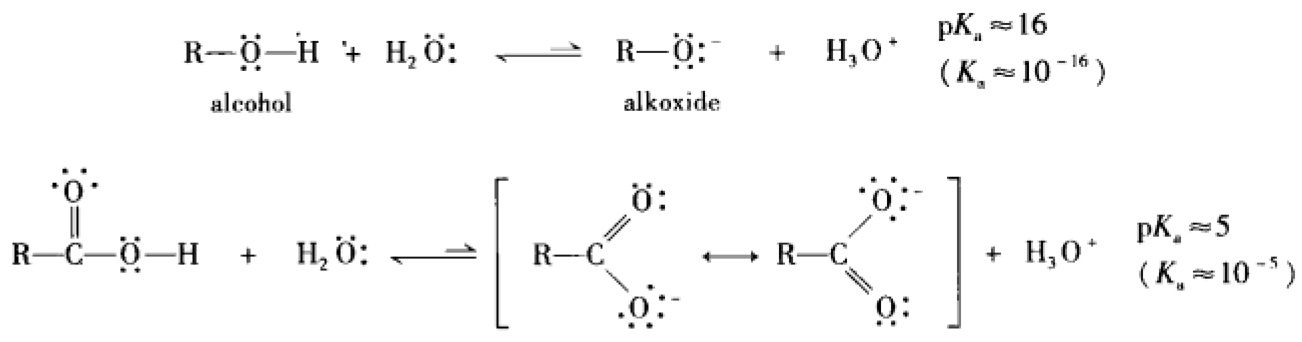


Figure 21-1 Stability of carboxylate ions.

The carboxylate ion can be visualized either as a resonance hybrid (as in Figure 21-1) or as a conjugated system of three *p* orbitals containing four electrons. The carbon atom and the two oxygen atoms are sp^2 hybridized, and each has an unhybridized *p* orbital. Overlap of these three *p* orbitals gives a three-center π molecular orbital system. There is half a π bond between the carbon and each oxygen atom, and there is half a negative charge on each oxygen atom (Figure 21-2).

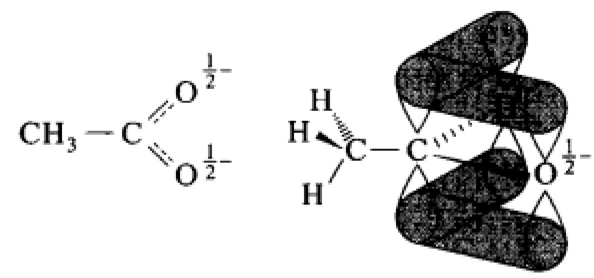
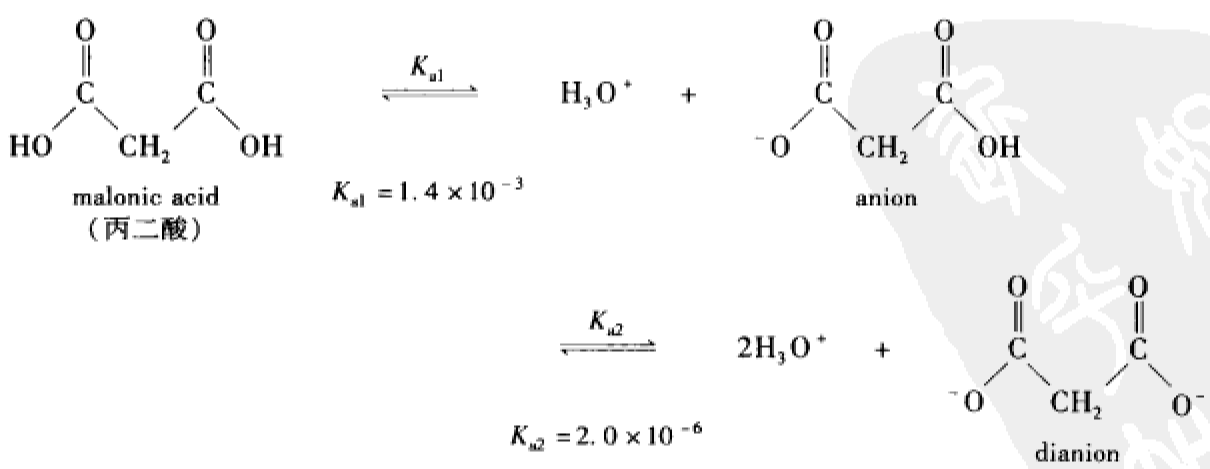


Figure 21-2 Structure of the acetate ions.

Table 21-3 gives pK_a values for dicarboxylic acids in addition to those for simple carboxylic acids. Diacids have two dissociation constants: K_{a1} is for the first dissociation, and K_{a2} is for the second dissociation, to give a dianion. The second carboxyl group is always less acidic than the first ($K_{a2} \ll K_{a1}$) because extra energy is required to create a second negative charge close to another, mutually repulsive, negative charge.



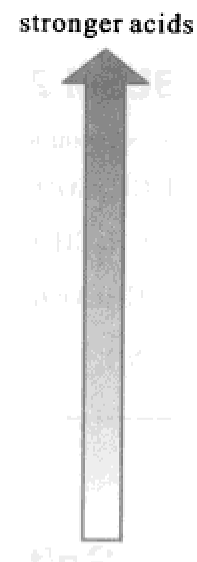
21-3B Substituent Effects on Acidity

A substituent that stabilizes the negatively charged carboxylate ion promotes dissociation and results in a stronger

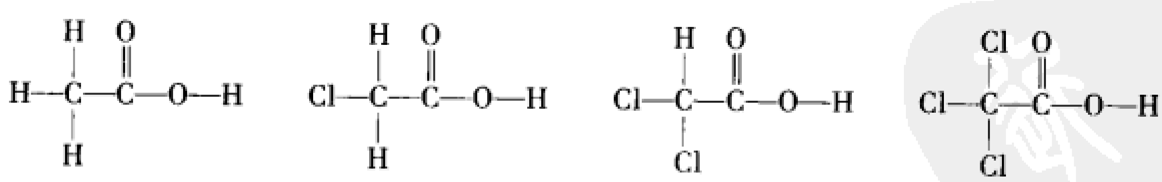
acid. Electronegative atoms enhance the strength of an acid in this manner. This inductive effect can be quite large if one or more strongly electron-withdrawing groups are present on the α carbon atom. For example, chloroacetic acid ($ClCH_2$—COOH) has a pK_a of 2.86, indicating that it is a stronger acid than acetic acid (pK_a = 4.74). Dichloroacetic acid (Cl_2CH—COOH) is stronger yet, with a pK_a of 1.26. Trichloroacetic acid (Cl_3C—COOH) has a pK_a of 0.64, comparable in strength to some mineral acids. Table 21-4 lists values of K_a and pK_a for some substituted carboxylic acids, showing how electron-withdrawing groups enhance the strength of an acid.

TABLE 21-4 Values of K_a and pK_a for Substituted Carboxylic Acids

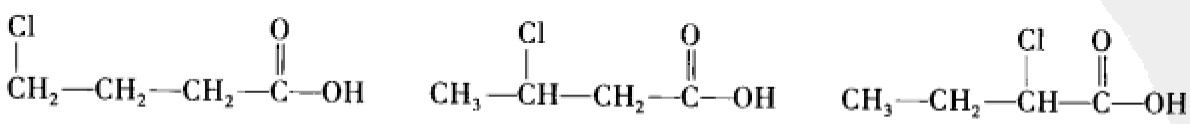
Acid	K_a	pK_a
F_3CCOOH	5.9×10^{-1}	0.23
Cl_3CCOOH	2.3×10^{-1}	0.64
$Cl_2CHCOOH$	5.5×10^{-2}	1.26
O_2N—CH_2COOH	2.1×10^{-2}	1.68
$NCCH_2COOH$	3.4×10^{-3}	2.46
FCH_2COOH	2.6×10^{-3}	2.59
$ClCH_2COOH$	1.4×10^{-3}	2.86
$CH_3CH_2CHClCOOH$	1.4×10^{-3}	2.86
$BrCH_2COOH$	1.3×10^{-3}	2.90
ICH_2COOH	6.7×10^{-4}	3.18
$HC{\equiv}CCH_2COOH$	4.8×10^{-4}	3.32
CH_3OCH_2COOH	2.9×10^{-4}	3.54
$HOCH_2COOH$	1.5×10^{-4}	3.83
$CH_3CHClCH_2COOH$	8.9×10^{-5}	4.05
$C_6H_5CH_2COOH$	4.9×10^{-5}	4.31
$CH_2{=}CHCH_2COOH$	4.5×10^{-5}	4.35
$ClCH_2CH_2CH_2COOH$	3.0×10^{-5}	4.52
CH_3COOH	1.8×10^{-5}	4.74
$CH_3CH_2CH_2COOH$	1.5×10^{-5}	4.82
CH_3CH_2COOH	1.3×10^{-5}	4.89



The magnitude of a substituent effect depends on its distance from the carboxyl group. Substituents on the α carbon atom are most effective in increasing acid strength. More distant substituents have smaller effects on acidity, showing that inductive effects decrease rapidly with distance.

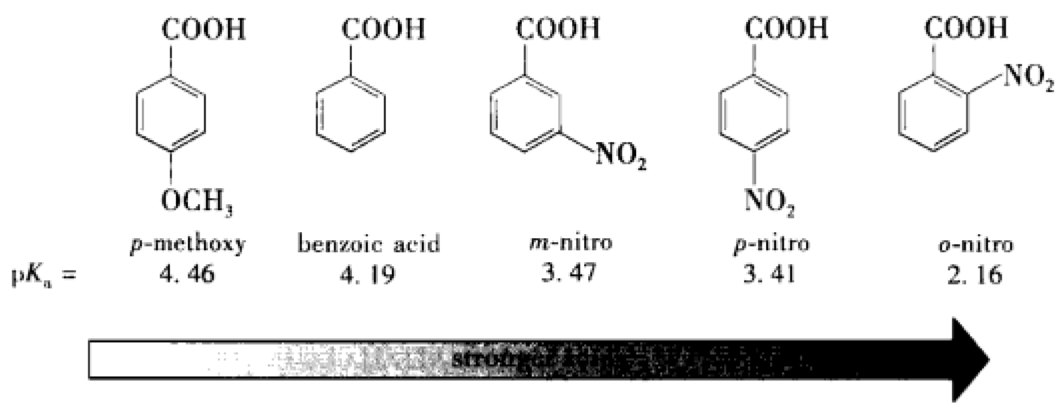


acetic acid (乙酸) pK_a = 4.74 | chloroacetic acid pK_a = 2.86 | dichloroacetic acid pK_a = 1.26 | trichloroacetic acid pK_a = 0.64



4-chlorobutanoic acid pK_a = 4.52 | 3-chlorobutanoic acid pK_a = 4.05 | 2-chlorobutanoic acid pK_a = 2.86

Substituted benzoic acids show similar trends in acidity, with electron-withdrawing groups enhancing the acid strength and electron-donating groups decreasing the acid strength. These effects are strongest for substituents in the ortho and para positions. In the examples shown below, notice that a nitro substituent (electron-withdrawing) increases the strength of the acid, while a methoxyl substituent (electron-donating) decreases the acid strength. The nitro group has a larger effect in the ortho and para positions than in the meta position.



PROBLEM 21-1

Rank the compounds in each set in order of increasing acid strength.

(a) CH_3CH_2COOH $CH_3CHBrCOOH$ CH_3CBr_2COOH

(b) $CH_3CH_2CH_2CHBrCOOH$ $CH_3CH_2CHBrCH_2COOH$ $CH_3CHBrCH_2CH_2COOH$

(c) $CH_3CH(NO_2)COOH$ $CH_3CH(Cl)COOH$ CH_3CH_2COOH $CH_3CH(C{\equiv}N)COOH$

21-4 Salts of Carboxylic Acids

A strong base can completely deprotonate a carboxylic acid. The products are a carboxylate ion, the cation remaining from the base, and water. The combination of a carboxylate ion and a cation is a **salt of a carboxylic acid**.

$$\underset{\text{carboxylic acid}}{R{-}C({=}O){-}O{-}H} + \underset{\text{strong base}}{M^{+}\ {}^{-}OH} \rightleftharpoons \underset{\text{acid salt}}{R{-}C({=}O){-}O^{-}\ {}^{+}M} + \underset{\text{water}}{H_2O}$$

For example, sodium hydroxide deprotonates acetic acid to form sodium acetate, the sodium salt of acetic acid.

$$\underset{\text{acetic acid}}{CH_3{-}C({=}O){-}O{-}H} + \underset{\text{sodium hydroxide}}{Na^{+}\ {}^{-}OH} \rightleftharpoons \underset{\text{sodium acetate}}{CH_3{-}C({=}O){-}O^{-}\ {}^{+}Na} + H_2O$$

［乙酸;醋酸(俗)］

Because mineral acids are stronger than carboxylic acids, addition of a mineral acid converts a carboxylic acid salt back to the original carboxylic acid.

$$\underset{\text{acid salt}}{R{-}C({=}O){-}O^{-}\ {}^{+}M} + H^{+} \rightleftharpoons \underset{\text{regenerated acid}}{R{-}C({=}O){-}O{-}H} + M^{+}$$

Example

$$\underset{\text{sodium acetate}}{CH_3-\overset{\overset{\Large O}{\|}}{C}-O^-\,{}^+Na} + H^+Cl^- \rightleftharpoons \underset{\text{acetic acid}}{CH_3-\overset{\overset{\Large O}{\|}}{C}-O-H} + Na^+Cl^-$$

Carboxylic acid salts have very different properties from the acids, including enhanced solubility in water and less odor. Because acids and their salts are easily interconverted, these salts serve as useful derivatives of carboxylic acids.

Properties of Acid Salts Like the salts of amines, carboxylic acid salts are solids with little odor. They generally melt at high temperatures, and they often decompose before reaching their melting points. Carboxylate salts of the alkali metals (Li^+, Na^+, K^+) and ammonium (NH_4^+) carboxylates are generally soluble in water but relatively insoluble in nonpolar organic solvents. *Soap* is a common example of carboxylate salts, consisting of the soluble sodium salts of long-chain fatty acids. Carboxylate salts of most other metal ions are insoluble in water. For example, when soap is used in "hard" water containing calcium, magnesium, or iron ions, the insoluble carboxylate salts precipitate out as "hard-water scum."

$$\underset{\text{a soap}}{2CH_3(CH_2)_{16}-\overset{\overset{\Large O}{\|}}{C}-O^-\,{}^+Na} + Ca^{2+} \longrightarrow \underset{\text{"hard-water scum"}}{[CH_3(CH_2)_{16}-\overset{\overset{\Large O}{\|}}{C}-O]_2Ca\downarrow} + 2Na^+$$

Salt formation can be used to identify and purify acids. Carboxylic acids are deprotonated by the weak base sodium bicarbonate, forming the sodium salt of the acid, carbon dioxide, and water. An unknown compound that is insoluble in water, but dissolves in a sodium bicarbonate solution with a release of bubbles of carbon dioxide, is almost certainly a carboxylic acid.

$$\underset{\text{insoluble in water}}{R-\overset{\overset{\Large O}{\|}}{C}-O-H} + NaHCO_3 \rightleftharpoons \underset{\text{water soluble}}{R-\overset{\overset{\Large O}{\|}}{C}-O^-\,{}^+Na} + H_2O + CO_2\uparrow$$

Some purification methods take advantage of the different solubilities of acids and their salts. Nonacidic (or weakly acidic) impurities can be removed from a carboxylic acid using acid-base extractions (Figure 21-3). First, the acid is dissolved in an organic solvent such as ether and shaken with water. The acid remains in the organic phase while any water-soluble impurities are washed out. Next, the acid is washed with aqueous sodium bicarbonate, forming a salt that dissolves in the aqueous phase. Nonacidic impurities (and weakly acidic impurities such as phenols) remain in the ether phase. The phases are separated, and acidification of the aqueous phase regenerates the acid, which is insoluble in water but dissolves in a fresh portion of ether. Evaporation of the final ether layer gives the purified acid.

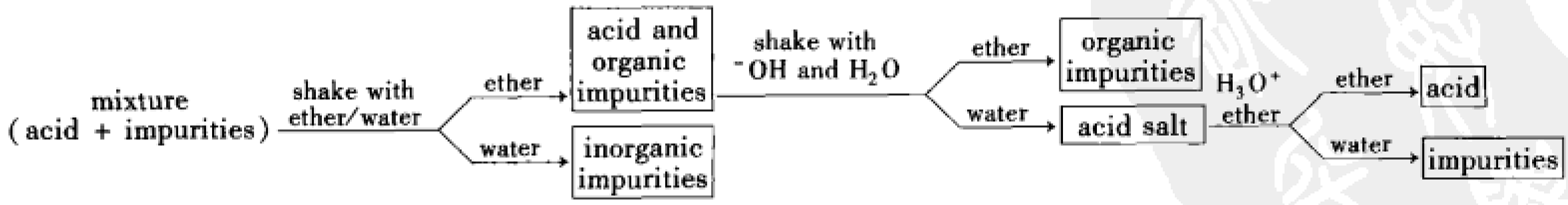


Figure 21-3 The solubility properties of acids and their salts may be used to remove nonacidic impurities.

PROBLEM 21-2

Suppose you have just synthesized heptanoic acid from 1-heptanol. The product is contaminated by sodium dichromate, sulfuric acid, 1-heptanol, and possibly heptanal. Explain how you would use acid-base extractions to purify the heptanoic acid. Use a chart like that in Figure 21-3 to show where the impurities are at each stage.

PROBLEM 21-3

Phenols are less acidic than carboxylic acids, with values of pK_a around 10. Phenols are deprotonated by (and therefore soluble in) solutions of sodium hydroxide but not by solutions of sodium bicarbonate. Explain how you would use extractions to isolate the three pure compounds from a mixture of *p*-cresol (*p*-methylphenol), cyclohexanone, and benzoic acid.

PROBLEM 21-4

Oxidation of a primary alcohol to an aldehyde usually gives some over-oxidation to the carboxylic acid. Assume you have used PCC to oxidize 1-pentanol to pentanal.

(a) Show how you would use acid-base extraction to purify the pentanal.

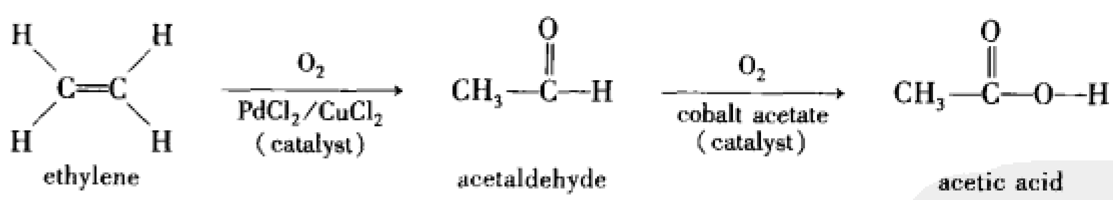
(b) Which of the expected impurities cannot be removed from pentanal by acid-base extractions? How would you remove this impurity?

21-5 Commercial Sources of Carboxylic Acids

The most important commercial aliphatic acid is acetic acid. *Vinegar* is a 5% aqueous solution of acetic acid used in cooking and in prepared foods such as pickles, ketchup, and salad dressings. Vinegar is produced by fermentation of sugars and starches. An intermediate in this fermentation is ethyl alcohol. When fermented alcoholic beverages such as wine and cider are exposed to air, the alcohol oxidizes to acetic acid. This is the source of "wine vinegar" and "cider vinegar."

$$\text{sugar and starches} \xrightarrow{\text{fermentation}} \underset{\text{ethyl alcohol}}{CH_3-CH_2-OH} \xrightarrow[O_2]{\text{fermentation}} \underset{\text{vinegar (醋)}}{CH_3-\overset{\overset{\large O}{\|}}{C}-OH}$$

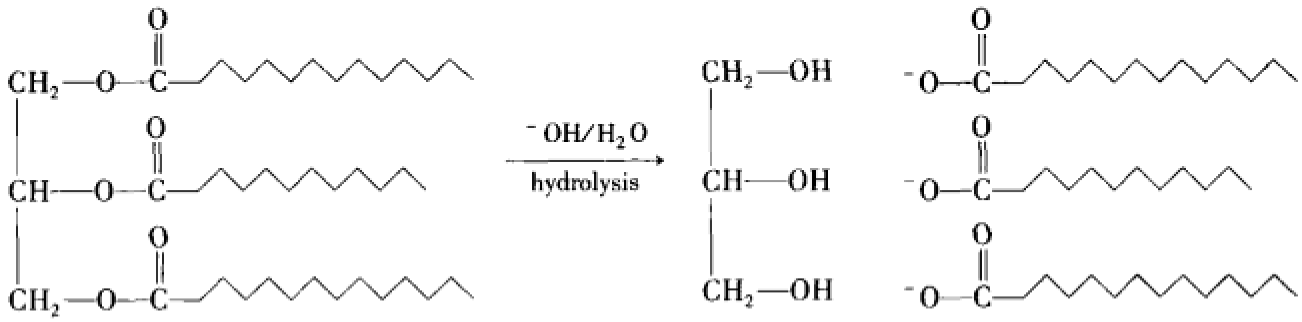
Acetic acid is also an industrial chemical. It serves as a solvent, a starting material for synthesis, and a catalyst for a wide variety of reactions. Some industrial acetic acid is produced from ethylene, using a catalytic oxidation to form acetaldehyde, followed by another catalytic oxidation to acetic acid.



Methanol can also serve as the feedstock for an industrial synthesis of acetic acid. The rhodium-catalyzed reaction of methanol with carbon monoxide requires high pressures, so it is not suitable for a laboratory synthesis.

$$\underset{\text{methanol}}{CH_3OH} + CO \xrightarrow[\text{heat, pressure}]{\text{Rh catalyst}} \underset{\text{acetic acid}}{CH_3COOH}$$

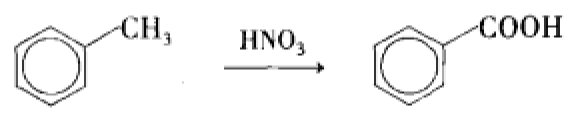
Figure 21-4 shows how long-chain aliphatic acids are obtained from the hydrolysis of fats and oils, a reaction discussed in Chapter 26. The **fatty acids** found in fats and oils are generally straight-chain acids with even numbers of carbon atoms ranging between about C_6 and C_{18}. The hydrolysis of animal fat gives mostly saturated fatty acids; plant oils give large amounts of unsaturated fatty acids with one or more olefinic double bonds.



fat or oil — glycerol (甘油) — fatty acid salts (soap)

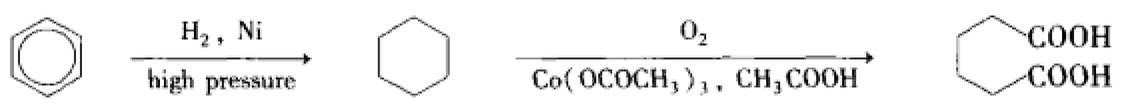
Figure 21-4 Hydrolysis of a fat or an oil gives a mixture of the salts of straight-chain fatty acids.

Some aromatic carboxylic acids are also commercially important. Benzoic acid is used as an ingredient in medications, a preservative in foods, and a starting material for synthesis. Benzoic acid can be produced by the oxidation of toluene with potassium permanganate, nitric acid, or other strong oxidants.

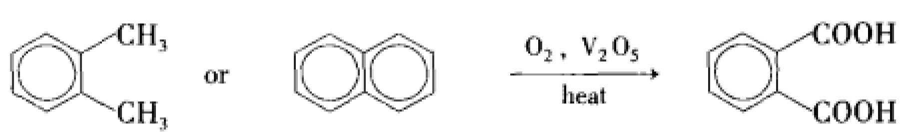


toluene (甲苯) — benzoic acid

Two important commercial diacids are adipic acid (hexanedioic acid) and phthalic acid (1,2-benzenedicarboxylic acid). Adipic acid is used in the manufacture of nylon 66, and phthalic acid is used to make polyesters. The industrial synthesis of adipic acid uses benzene as the starting material. Benzene is hydrogenated to cyclohexane, whose oxidation (using a cobalt/acetic acid catalyst) gives adipic acid. Phthalic acid is produced by the direct oxidation of naphthalene or xylene using a vanadium pentoxide catalyst.



benzene — cyclohexane — adipic acid (己二酸)

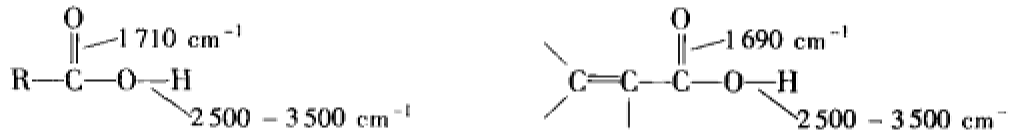


xylene (二甲苯) — naphthalene (萘) — phthalic acid (邻苯二甲酸)

21-6 Spectroscopy of Carboxylic Acids

21-6A Infrared Spectroscopy

The most obvious feature in the infrared spectrum of a carboxylic acid is the intense carbonyl stretching absorption. In a saturated acid, this vibration occurs around 1 710 cm^{-1}, often broadened by hydrogen bonding involving the carbonyl group. In conjugated acids, the carbonyl stretching frequency is lowered to about 1 690 cm^{-1}



The O—H stretching vibration of a carboxylic acid absorbs in a broad band around 2 500–3 500 cm^{-1}. This frequency range is lower than the hydroxyl stretching frequencies of water and alcohols, whose O—H groups

absorb in a band centered around 3 300 cm^{-1}. In the spectrum of a carboxylic acid, the broad hydroxyl band appears right on top of the C—H stretching region. This overlapping of absorptions gives the 3 000 cm^{-1} region a characteristic appearance of a broad peak (the O—H stretching) with sharp peaks (C—H stretching) superimposed on it.

21-6B NMR Spectroscopy

Carboxylic acid protons are the most deshielded protons we have encountered, absorbing between $\delta 10$ and $\delta 13$. Depending on the solvent and the concentration, this acid proton peak may be sharp or broad, but it is always unsplit because of proton exchange.

The protons on the α carbon atom absorb between $\delta 2.0$ and $\delta 2.5$, in about the same position as the protons on a carbon atom alpha to a ketone or an aldehyde.

21-6C Ultraviolet Spectroscopy

Saturated carboxylic acids have a weak $n \rightarrow \pi^*$ transition that absorbs around 200 to 215 nm. This absorption corresponds to the weak transition around 270 to 300 nm in the spectra of ketones and aldehydes. The molar absorptivity is very small (about 30 to 100), and the absorption often goes unnoticed.

Conjugated acids show much stronger absorptions. One C=C double bond conjugated with the carboxyl group results in a spectrum with λ_{max} still around 200 nm, but with molar absorptivity of about 10 000 L/(mol·cm). A second conjugated double bond raises the value of λ_{max} to about 250 nm, as illustrated by the following examples:

$$CH_2{=}CH{-}C({=}O){-}OH \qquad \lambda_{max} = 200 \text{ nm} \qquad \kappa = 10\,000 \text{ L/(mol·cm)}$$

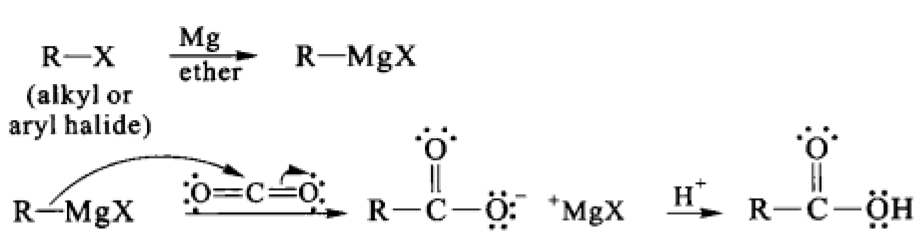
$$CH_3{-}CH{=}CH{-}CH{=}CH{-}C({=}O){-}OH \qquad \lambda_{max} = 254 \text{ nm} \qquad \kappa = 25\,000 \text{ L/(mol·cm)}$$

21-7 Synthesis of Carboxylic Acids

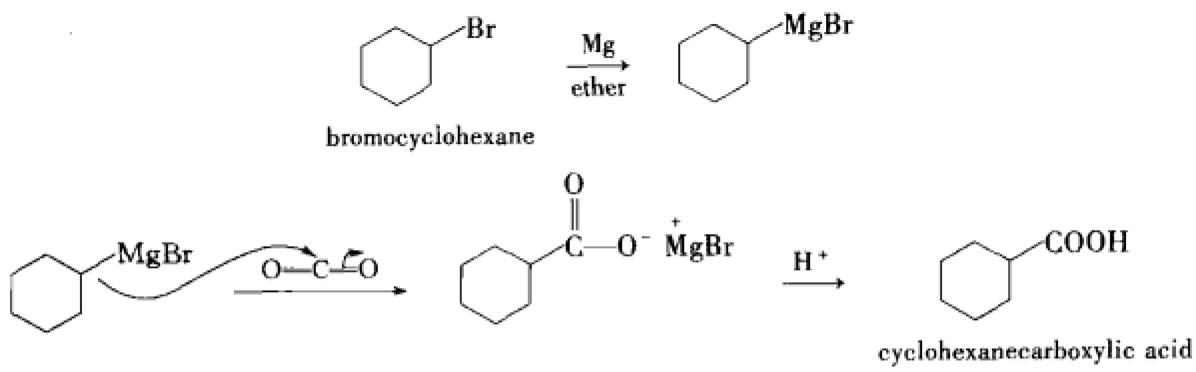
We have already encountered three methods for preparing carboxylic acids: (1) oxidation of alcohols and aldehydes, (2) oxidative cleavage of alkenes and alkynes, and (3) severe side-chain oxidation of alkylbenzenes. In the following section, we consider additional syntheses of carboxylic acid that we have not covered before.

21-7A Carboxylation of Grignard Reagents

We have seen how Grignard reagents act as strong nucleophiles, adding to the carbonyl groups of ketones and aldehydes. Similarly, Grignard reagents add to carbon dioxide to form magnesium salts of carboxylic acids. Addition of dilute acid protonates these magnesium salts to give carboxylic acids. This method is useful because it converts a halide functional group to a carboxylic acid functional group with an additional carbon atom.



Example



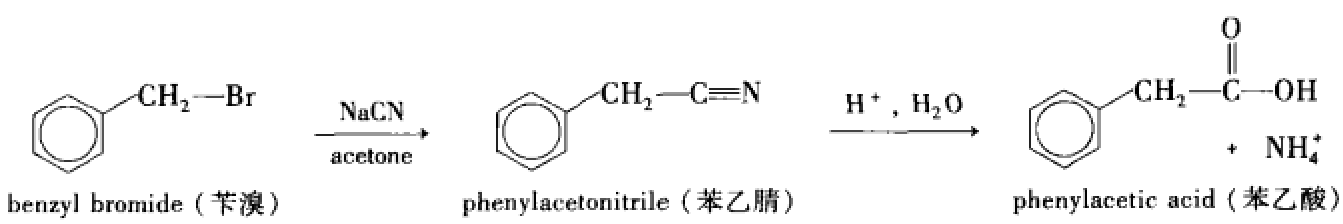
21-7B Formation and Hydrolysis of Nitriles

Another way to convert an alkyl halide (or tosylate) to a carboxylic acid with an additional carbon atom is to displace the halide with sodium cyanide. The product is a nitrile with one additional carbon atom. Acidic or basic hydrolysis of the nitrile gives a carboxylic acid. This method is limited to halides and tosylates that are good S_N2 electrophiles: usually primary and unhindered.

$$\text{R—CH}_2\text{—X} \xrightarrow[\text{acetone}]{\text{NaCN}} \text{R—CH}_2\text{—C}{\equiv}\text{N:}$$

$$\text{R—CH}_2\text{—C}{\equiv}\text{N:} \xrightarrow[\text{or }^-\text{OH, H}_2\text{O}]{\text{H}^+\text{, H}_2\text{O}} \text{R—CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—OH} \quad + \quad \text{NH}_4^+$$

Example



PROBLEM 21-5

Show how you would synthesize the following carboxylic acids, using the indicated starting materials.

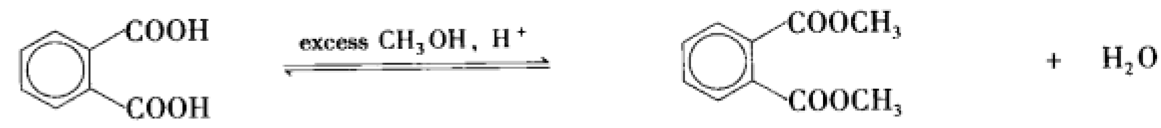
(**a**) 4-octyne → butanoic acid
(**b**) *trans*-cyclodecene → decanedioic acid
(**c**) bromobenzene → phenylacetic acid
(**d**) 2-butanol → 2-methylbutanoic acid
(**e**) *p*-xylene → terephthalic acid
(**f**) allyl iodide → 3-butenoic acid

21-8 Condensation of Acids with Alcohols: The Fischer Esterification

The **Fischer esterification** converts carboxylic acids and alcohols directly to esters by an acid-catalyzed nucleophilic acyl substitution. The net reaction is replacement of the acid —OH group by the —OR group of the alcohol.

$$\underset{\text{acid}}{\text{R—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—OH}} \quad + \quad \underset{\text{alcohol}}{\text{R}'\text{—OH}} \quad \overset{\text{H}^+}{\rightleftharpoons} \quad \underset{\text{ester}}{\text{R—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—O—R}'} \quad + \quad \text{H}_2\text{O}$$

Examples



phthalic acid (邻苯二甲酸) dimethyl phthalate (邻苯二甲酸二甲酯)

The Fischer esterification mechanism (see the Key Mechanism 21-1) is an acidcatalyzed nucleophilic acyl substitution. The carbonyl group of a carboxylic acid is not sufficiently electrophilic to be attacked by an alcohol. The acid catalyst protonates the carbonyl group and activates it toward nucleophilic attack. Loss of a proton gives the hydrate of an ester.

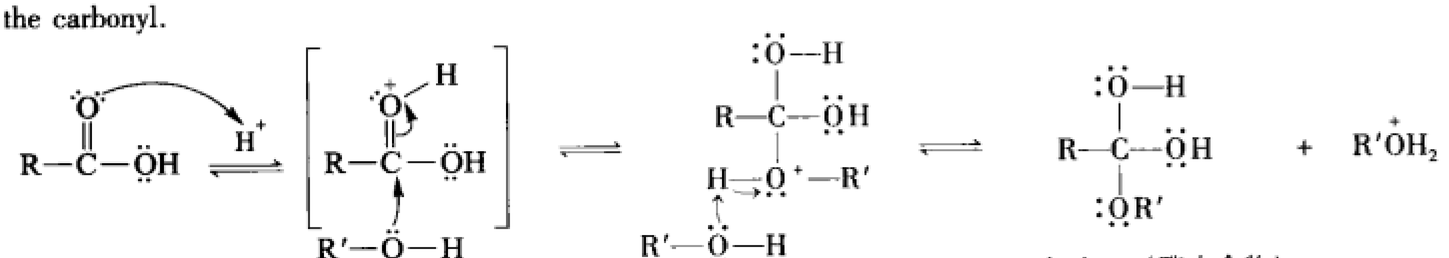
Loss of water from the hydrate of the ester occurs by the same mechanism as loss of water from the hydrate of a ketone. Protonation of either one of the hydroxyl groups allows it to leave as water, forming a resonance-stabilized cation. Loss of a proton from the second hydroxyl group gives the ester.

The mechanism of the Fischer esterification would seem long and complicated if you tried to memorize it, but we can understand it by breaking it down into two simpler mechanisms: (1) acid-catalyzed addition of the alcohol to the carbonyl and (2) acid-catalyzed dehydration. If you understand these mechanistic components, you can write the Fischer esterification mechanism without having to memorize it.

KEY MECHANISM 21-1 Fischer Esterification

***Part 1**: Acid-catalyzed addition of the alcohol to the carbonyl group.*

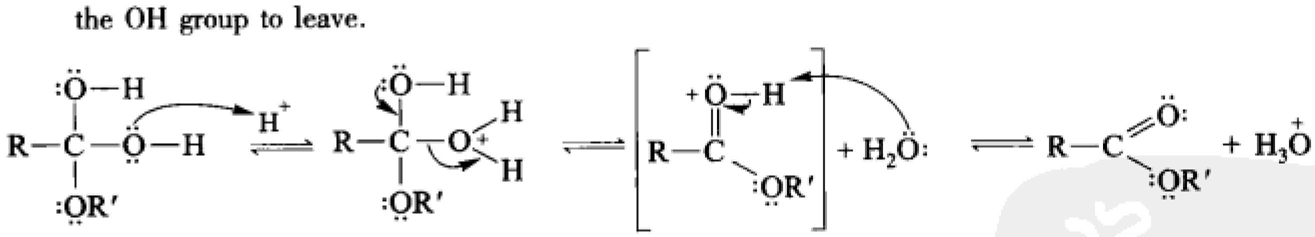
Protonation activates the carbonyl. The alcohol adds. Deprotonation completes the reaction.



ester hydrate (酯水合物)

***Part 2**: Acid-catalyzed dehydration.*

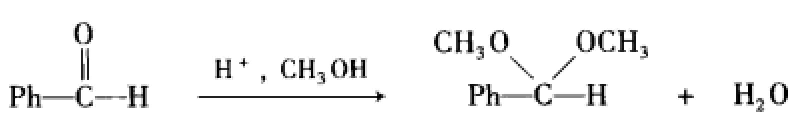
Protonation prepares the OH group to leave. Water leaves. Deprotonation completes the reaction.



QUESTION: Why can't the Fischer esterification take place under basic catalysis?

PROBLEM 21-6

Most of the Fischer esterification mechanism is identical with the mechanism of acetal formation. The difference is in the final step, where a carbocation loses a proton to give the ester. Write mechanisms for the following reactions, with the comparable steps directly above and below each other. Explain why the final step of the esterification (proton loss) cannot occur in acetal formation, and show what happens instead.



aldehyde acetal (缩醛)

$$\underset{\text{acid}}{\mathrm{Ph{-}C({=}O){-}OH}} \xrightarrow{\mathrm{H^+,\ CH_3OH}} \underset{\text{ester}}{\mathrm{Ph{-}C({=}O){-}OCH_3}} + \mathrm{H_2O}$$

PROBLEM 21-7

A carboxylic acid has two oxygen atoms, each with two nonbonding pairs of electrons.

(a) Draw the resonance forms of a carboxylic acid that is protonated on the hydroxyl oxygen atom.

(b) Compare the resonance forms with those given previously for an acid protonated on the carbonyl oxygen atom.

(c) Explain why the carbonyl oxygen atom of a carboxylic acid is more basic than the hydroxyl oxygen.

Fischer esterification is an equilibrium, and typical equilibrium constants for esterification are not very large. For example, if 1 mol of acetic acid is mixed with 1 mol of ethanol, the equilibrium mixture contains 0.65 mol each of ethyl acetate and water and 0.35 mol each of acetic acid and ethanol. Esterification using secondary and tertiary alcohols gives even smaller equilibrium constants.

Equilibrium mixture

$$\underset{0.35\ \text{mol}}{\mathrm{CH_3{-}C({=}O){-}OH}} + \underset{0.35\ \text{mol}}{\mathrm{CH_3CH_2OH}} \xrightleftharpoons{K_{eq}=3.38} \underset{0.65\ \text{mol}}{\mathrm{CH_3{-}C({=}O){-}OCH_2CH_3}} + \underset{0.65\ \text{mol}}{\mathrm{H_2O}}$$

Esterification may be driven to the right either by using an excess of one of the reactants or by removing one of the products. For example, in forming ethyl esters, excess ethanol is often used to drive the equilibrium as far as possible toward the ester. Alternatively, water may be removed either by distilling it out or by adding a dehydrating agent such as magnesium sulfate or **molecular sieves** (dehydrated zeolite crystals that adsorb water).

Because of the inconvenience of driving the Fischer esterification to completion, we might prefer the reaction of an acid chloride with an alcohol for the laboratory synthesis of esters. The Fischer esterification is preferred in industry, however, where the techniques mentioned give good yields of products and avoid the expensive step of converting the acid to its acid chloride.

PROBLEM 21-8

Show how Fischer esterification might be used to form the following esters. In each case, suggest a method for driving the reaction to completion.

(a) methyl salicylate (b) methyl formate (bp 32 ℃) (c) ethyl benzoate

PROBLEM 21-9

The mechanism of the Fischer esterification was controversial until 1938, when Irving Roberts and Harold Urey of Columbia University used isotopic labeling to follow the alcohol oxygen atom through the reaction. A catalytic amount of sulfuric acid was added to a mixture of 1 mol of acetic acid and 1 mol of special methanol containing the heavy ^{18}O isotope of oxygen. After a short period, the acid was neutralized to stop the reaction, and the components of the mixture were separated.

$$\mathrm{CH_3{-}C({=}O){-}O{-}H} + \mathrm{CH_3{-}{}^{18}O{-}H} \xrightleftharpoons{\mathrm{H_2SO_4}} \mathrm{CH_3{-}C({=}O){-}O{-}CH_3} + \mathrm{H_2O}$$

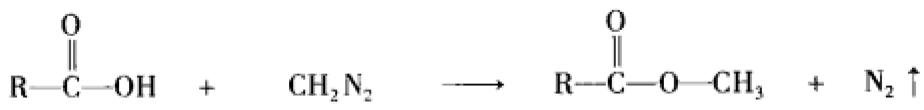
(a) Propose a mechanism for this reaction.

(b) Follow the labeled ^{18}O atom through your mechanism, and show where it will be found in the products.

(c) The ^{18}O isotope is not radioactive. Suggest how you could experimentally determine the amounts of ^{18}O in the separated components of the mixture.

21 − 9 Esterification Using Diazomethane

Carboxylic acids are converted to their methyl esters very simply by adding an ether solution of diazomethane. The only byproduct is nitrogen gas, and any excess diazomethane also evaporates. Purification of the ester usually involves only evaporation of the solvent. Yields are nearly quantitative in most cases.



acid diazomethane (重氮甲烷) methyl ester

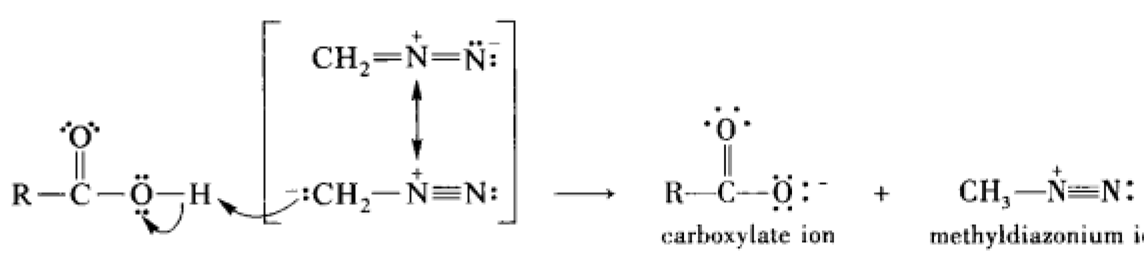
Example

cyclobutanecarboxylic acid methyl cyclobutanecarboxylate (100%)

Diazomethane is a toxic, explosive yellow gas that dissolves in ether and is fairly safe to use in ether solutions. The reaction of diazomethane with carboxylic acids probably involves transfer of the acid proton, giving a methyldiazonium salt. This diazonium salt is an excellent methylating agent, with nitrogen gas as a leaving group.

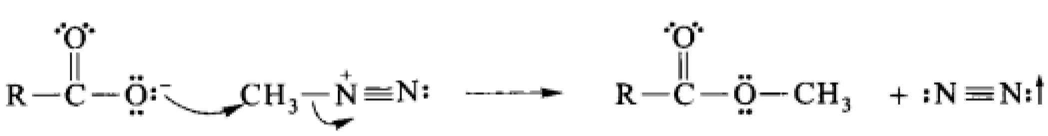
MECHANISM 21 − 2 Esterification Using Diazomethane

Step 1: Proton transfer, forming a carboxylate ion and a methyldiazonium ion.



carboxylate ion methyldiazonium ion

Step 2: Nucleophilic attack on the methyl group displaces nitrogen.

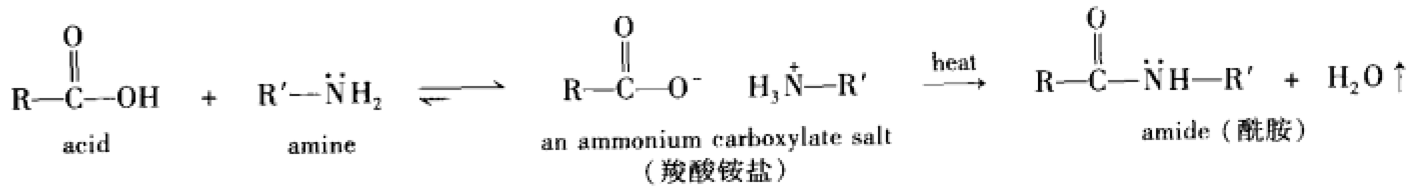


Because diazomethane is hazardous in large quantities, it is rarely used industrially or in large-scale laboratory reactions. The yields of methyl esters are excellent, however, so diazomethane is often used for small-scale esterifications of valuable and delicate carboxylic acids.

21 − 10 Condensation of Acids with Amines: Direct Synthesis of Amides

Amides can be synthesized directly from carboxylic acids, using heat to drive off water and force the reaction to completion. The initial acid-base reaction of a carboxylic acid with an amine gives an ammonium carboxylate salt. The carboxylate ion is a poor electrophile, and the ammonium ion is not nucleophilic, so the reaction stops

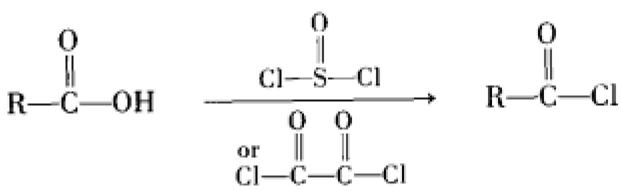
at this point. Heating this salt to well above 100 ℃ drives off steam and forms an amide. This direct synthesis is an important industrial process, and it often works well in the laboratory.



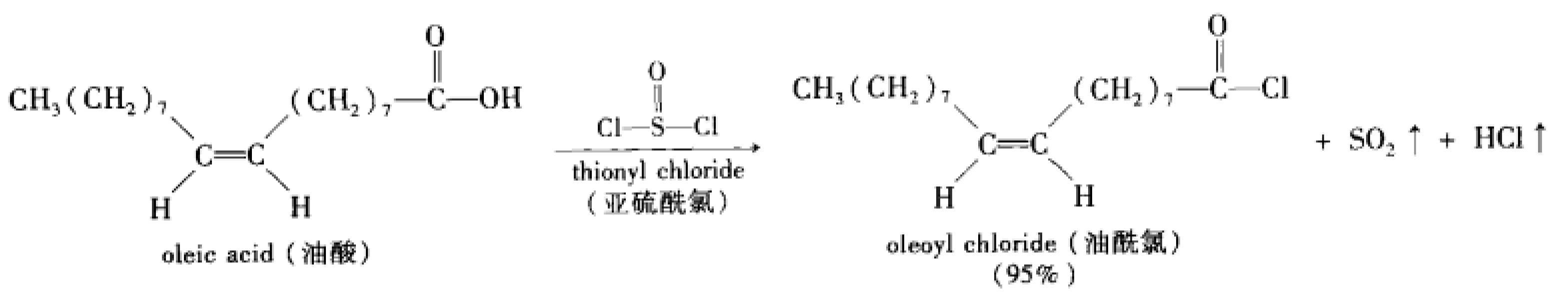
Example

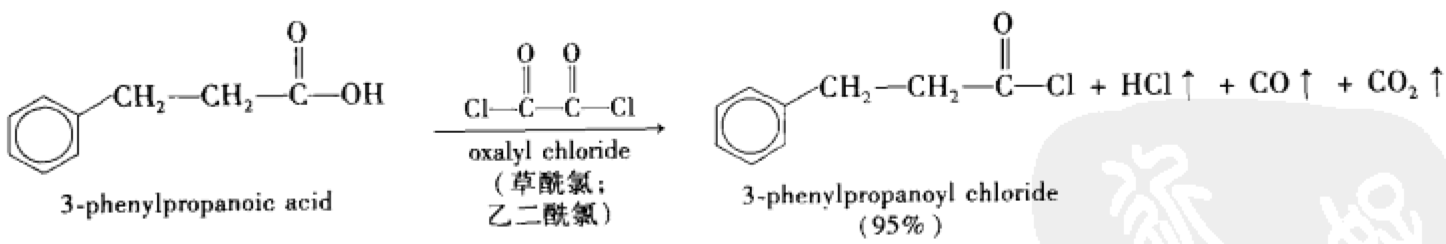
21-11 Formation of Acid Chlorides

The best reagents for converting carboxylic acids to acid chlorides are thionyl chloride ($SOCl_2$) and oxalyl chloride $(COCl)_2$ because they form gaseous byproducts that do not contaminate the product. Oxalyl chloride is particularly easy to use because it boils at 62 ℃ and any excess is easily evaporated from the reaction mixture.



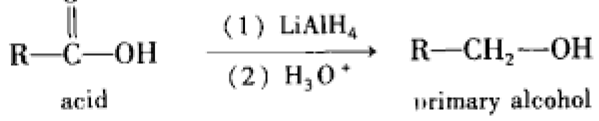
Examples



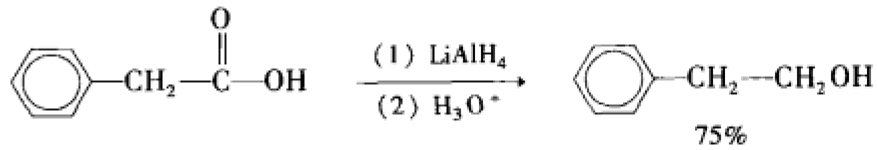


21-12 Reduction of Carboxylic Acids

Lithium aluminum hydride ($LiAlH_4$ or LAH) reduces carboxylic acids to primary alcohols. The aldehyde is an intermediate in this reduction, but it cannot be isolated because it is reduced more easily than the original acid.

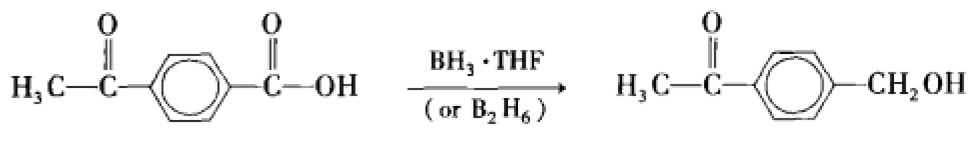


Example



phenylacetic acid 2-phenylethanol

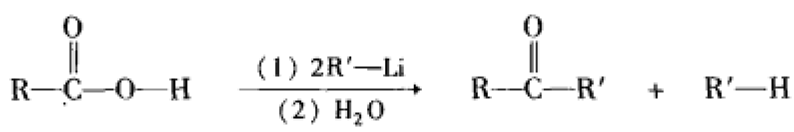
Borane also reduces carboxylic acids to primary alcohols. Borane (complex with THF) reacts with the carboxyl group faster than with any other carbonyl function. It often gives excellent selectivity, as shown by the following example, where a carboxylic acid is reduced while a ketone is unaffected. ($LiAlH_4$ would also reduce the ketone.)



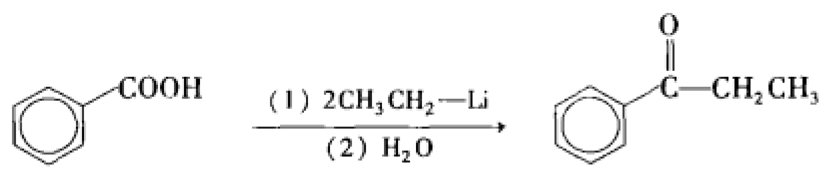
(80%)

21-13 Alkylation of Carboxylic Acids to Form Ketones

A general synthesis of ketones involves the reaction of a carboxylic acid with two equivalents of an organolithium reagent.

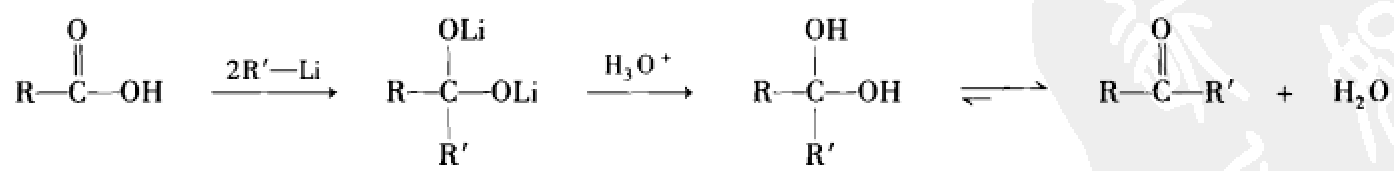


Example



benzoic acid propiophenone

The first equivalent of the organolithium reagent simply deprotonates the acid. The second equivalent adds to the carbonyl to give a stable dianion. Hydrolysis of the dianion (by adding water) gives the hydrate of a ketone. Because the ketone is formed in a separate hydrolysis step (rather than in the presence of the organolithium reagent), overalkylation is not observed.



carboxylic acid dianion hydrate of ketone ketone

PROBLEM 21-10

Show how the following ketones might be synthesized from the indicated acids, using any necessary reagents.

(a) propiophenone from propionic acid (two ways, using alkylation of the acid and using Friedel-Crafts acylation)

(b) methyl cyclohexyl ketone from cyclohexanecarboxylic acid

Summary in Chinese

本 章 概 要

一、羧酸的结构

羧基(—COOH)是羧酸的官能团,羧基中的碳原子为 sp^2 杂化,平面构型。三个 sp^2 杂化轨道分别与一个氧原子、一个羟基的氧原子和一个碳原子(在甲酸中是氢原子)形成三个 σ 键,键角约为 120°;sp^2 杂化碳原子的 p 轨道与两个氧原子的 p 轨道重叠,形成一个四电子三中心的 $p-\pi$ 共轭体系。

二、羧酸的物理性质

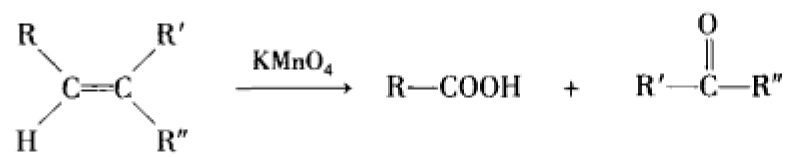
羧酸的沸点比相对分子质量相近的醇、醛、酮的要高,这是由于羧酸有较强的极性以及两个羧酸分子之间可通过两个氢键形成八元环的双分子缔合体,因此,常见的羧酸在固态或液态时,主要以双分子缔合体的形式存在。C_9 以上的羧酸一般是固体,但在碳链中含有双键,熔点下降。二元羧酸的熔点较高,一般是结晶体。低碳数的酸($\leqslant C_4$)由于分子极性大,与水分子可很好地形成氢键,与水能够互溶,随碳链增长,羧酸在水中溶解性下降。

三、羧酸的制备

1. 伯醇的氧化(oxidation of primary alcohols):

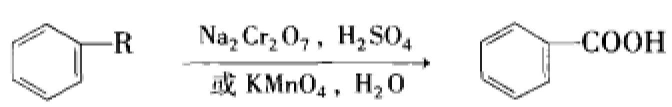
$$RCH_2OH \xrightarrow{KMnO_4} RCOOH$$

2. 烯、炔的氧化断裂(oxidation cleavage of alkenes and alkynes):



$$R—C\equiv C—R' \xrightarrow[\text{或}(1)\ O_3(2)\ H_2O]{KMnO_4} RCOOH + R'COOH$$

3. 烷基苯的氧化(oxidation of alkylbenzenes):



4. Grignard 试剂的羰基化(Carboxylation of Grignard reagents)

$$R—X + Mg \xrightarrow{\text{醚}} RMgX \xrightarrow{CO_2} R—\overset{O}{\overset{\|}{C}}—OMgX \xrightarrow{H^+} RCOOH$$

☆ 制备多一个碳原子的酸。

5. 腈的水解(hydrolysis of nitriles)

$$RCN \xrightarrow[\text{或 } OH^-,\ H_2O]{H^+,\ H_2O} RCOOH$$

6. 卤仿反应(haloform reaction, Section 23-3B):

$$R—\underset{\underset{O}{\|}}{C}—CH_3 \xrightarrow[X = Cl,\ Br,\ I]{X_2,\ OH^-} RCOO^- + HCX_3$$

☆ 用于制备少一个碳数的酸。

7. 丙二酸酯合成(malonic ester synthesis, Section 23－15)：

$$CH_2(COO\ Et)_2 \xrightarrow[(2)\ RX]{(1)\ NaOEt} RCH(COO\ Et)_2 \xrightarrow[(2)\ H^+,\Delta]{(1)\ OH^-} RCH_2COOH$$

四、羧酸的化学性质

1. 羧酸的酸性：羧酸的酸性比醇强，在脂肪族羧酸中，与羧基相连的烃基上有吸电子取代基时，羧酸酸性增强；吸电子取代基越多，且与羧酸距离越近，吸电子诱导效应越强，羧酸的酸性越强；二元羧酸的酸性比一元羧酸的酸性强，二元羧酸的第一步解离远远比第二步解离容易，即 $K_{a1} \gg K_{a2}$。在芳香羧酸中，苯环上连吸电子基，酸性增强，且吸电子基在羧酸的邻、对位上比在间位上酸性更强；给电子基在羧酸对位上，酸性减弱。

羧酸可与 NaOH、Na_2CO_3、$NaHCO_3$、$Ca(OH)_2$ 等反应生成羧酸盐，该盐再与酸如 HCl 作用，又可得到原来的羧酸，此反应可用于羧酸的分离、提纯。

$$RCOOH + NaOH \longrightarrow RCOONa \xrightarrow{HCl} RCOOH + NaCl$$

2. 与醇的反应－Fischer 酯化(Fischer esterification)：

$$RCOOH + R'OH \overset{H^+}{\rightleftharpoons} R-\overset{\overset{O}{\|}}{C}-OR' + H_2O$$

☆ 酸催化活化羧基中的羰基，有利于亲核试剂醇的进攻，碱不能催化该反应；可逆反应；可用于酯的制备。

3. 与重氮甲烷(diazomethane)的反应：

$$RCOOH + CH_2N_2 \longrightarrow RCOOCH_3 + N_2\uparrow$$

☆ 重氮甲烷是很好的甲基化试剂；该反应可用于制备羧酸甲酯，几乎定量进行。

4. 与二氯亚砜(thionyl chloride)的反应：

$$RCOOH + SOCl_2 \longrightarrow R-\overset{\overset{O}{\|}}{C}-Cl + SO_2\uparrow + HCl\uparrow$$

☆ 适合实验室制备酰氯。

5. 与胺的反应：

$$RCOOH + R'NH_2 \rightleftharpoons RCOO\overset{+}{N}H_3R' \xrightarrow{\Delta} R-\overset{\overset{O}{\|}}{C}-NHR' + H_2O$$

6. 与烷基锂(alkyllithium)的反应：

$$R-\overset{\overset{O}{\|}}{C}-OH + 2R'Li \longrightarrow R-\underset{\underset{R'}{|}}{\overset{\overset{OLi}{|}}{C}}-OLi \xrightarrow{H_3^+O} R-\underset{\underset{R'}{|}}{\overset{\overset{OH}{|}}{C}}-OH \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-R' + H_2O$$

☆ 可用于由羧酸制备酮。

7. 羧酸的还原：

$$R-\overset{\overset{O}{\|}}{C}-OH \xrightarrow[(2)\ H_3^+O]{(1)\ LiAlH_4} RCH_2OH$$

$$R-\overset{\overset{O}{\|}}{C}-OH \xrightarrow{BH_3\cdot THF} RCH_2OH$$

☆ $LiAlH_4$ 还原性强，对分子中的—NO_2、—CN、$-\overset{\displaystyle O}{\overset{\|}{C}}-Y$ 等均能还原，选择性差；$BH_3 \cdot THF$ 对—COOH有选择性还原，分子中存在的—NO_2、—CN、$-\overset{\displaystyle O}{\overset{\|}{C}}-$ 不被还原。

Essential Problem-Solving Skills in Chapter 21

1. Show how the acidity of acids varies with their substitution.
2. Contrast the physical properties of carboxylic acids and their salts.
3. Interpret the IR, UV, NMR, and mass spectra of carboxylic acids, and use the spectral information to determine the structures.
4. Show how to synthesize carboxylic acids from oxidation of alcohols and aldehydes, carboxylation of Grignard reagents, hydrolysis of nitriles, and oxidation of alkylbenzenes.
5. Show how acids are converted to esters and amides using acid chlorides as intermediates. Propose mechanisms for these nucleophilic acyl substitutions.
6. Give the mechanism of the Fischer esterification, and show how the equilibrium can be driven toward the products or the reactants.
7. Predict the products of reactions of carboxylic acids with the following reagents and give mechanisms where appropriate:
   (a) diazomethane
   (b) amines, followed by heating
   (c) lithium aluminum hydride
   (d) excess alkyllithium reagents

Study Problems

21-11 Define each term, and give an example.

(a) carboxylic acid (b) carboxylate ion (c) carboxylation of a Grignard reagent
(d) acid-dissociation constant (e) ester (f) Fischer esterification
(g) fatty acid (h) nucleophilic acyl substitution (i) dicarboxylic acid
(j) salt of a carboxylic acid (k) acid chloride (l) acid anhydride

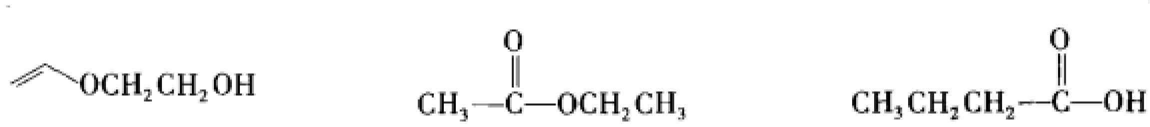
21-12 Arrange each group of compounds in order of increasing basicity.

(a) CH_3COO^-, $ClCH_2COO^-$, and PhO^-
(b) sodium acetylide, sodium amide, and sodium acetate
(c) sodium benzoate, sodium ethoxide, and sodium phenoxide
(d) pyridine, acetic acid, and ethanol

21-13 Predict the products (if any) of the following acid-base reactions.

(a) acetic acid + ammonia (b) phthalic acid + excess NaOH
(c) *p*-toluic acid + potassium trifluoroacetate (d) α-bromopropionic acid + sodium propionate
(e) benzoic acid + sodium phenoxide

21-14 Rank the following isomers in order of increasing boiling point, and explain the reasons for your order of ranking.



vinyloxyethanol ethyl acetate butyric acid

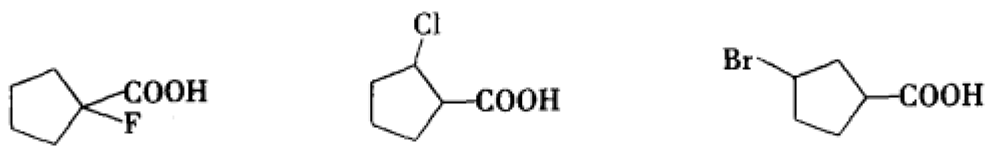
21-15 Arrange each group of compounds in order of increasing acidity.

(**a**) phenol, ethanol, acetic acid

(**b**) *p*-toluenesulfonic acid, acetic acid, chloroacetic acid

(**c**) benzoic acid, *o*-nitrobenzoic acid, *m*-nitrobenzoic acid

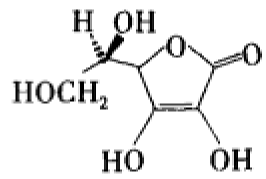
(**d**) butyric acid, α-bromobutyric acid, β-bromobutyric acid

(**e**) 

21-16 What conclusions can you draw from the pK_a values shown for the following compounds?

Compound	pK_a
CH_2COOH with NO_2	1.68
CH_2COOH with CN	2.46
CH_2COOH with Cl	2.86
CH_2COOH with OH	3.83
CH_2COOH with H	4.74

21-17 Given the structure of ascorbic acid (vitamin C):



ascorbic acid

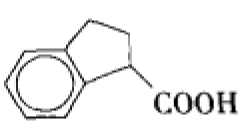
(**a**) Is ascorbic acid a carboxylic acid?

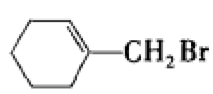
(**b**) Compare the acid strength of ascorbic acid (pK_a = 4.71) with acetic acid.

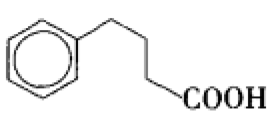
(**c**) Predict which proton in ascorbic acid is the most acidic.

(**d**) Draw the form of ascorbic acid that is present in the body (aqueous solution, pH = 7.4).

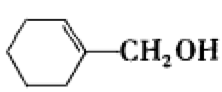
21-18 Predict the products, if any, of the following reactions.

(**a**)  $\xrightarrow[(2)\ H_3O^+]{(1)\ LiAlH_4}$

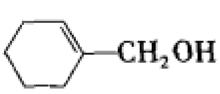
(**b**)  $\xrightarrow[(2)\ H_3O^+]{(1)\ NaCN}$

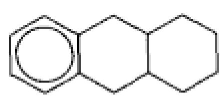
(**c**)  $\xrightarrow[(2)\ AlCl_3]{(1)\ SOCl_2}$

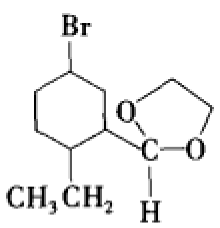
(**d**) 4-octyne $\xrightarrow[\text{(warm, concd.)}]{KMnO_4,\ H_2O}$

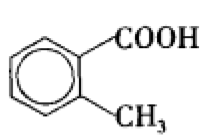
(**e**)  $\xrightarrow{Na_2Cr_2O_7,\ H_2SO_4}$

(**f**) $CH_3CH_2-CH(Ph)-COOH \xrightarrow{B_2H_6}$

(**g**)  $\xrightarrow[\text{(warm, concd.)}]{KMnO_4,\ H_2O}$

(**h**)  $\xrightarrow[\text{(hot, concd.)}]{KMnO_4,\ H_2O}$

(**i**)  $\xrightarrow[(3)\ H_3O^+]{(1)\ Mg,\ ether\ (2)\ CO_2}$

(**j**)  $\xrightleftharpoons{\text{2-butanol, } H^+}$

(**k**) $HOCH_2CH_2CH_2-\overset{O}{\overset{\|}{C}}-OH \xrightarrow{H^+}$ (cyclic ester)

21-19 Show how you would accomplish the following syntheses efficiently (you may use any necessary reagents).

(**a**) *trans*-1-bromo-2-butene → *trans*-3-pentenoic acid (two ways)

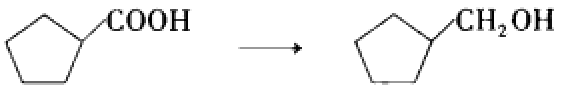
(**b**) 3-hexene → propanoic acid

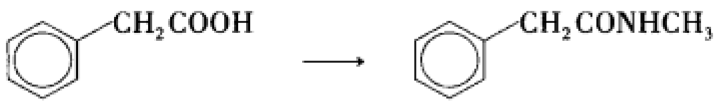
(**c**) 2-butenal → 2-butenoic acid

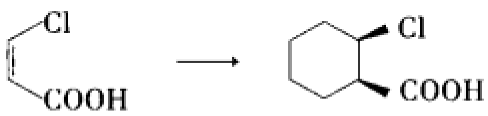
(**d**) hexanoic acid → hexanal

(e) $CH_3(CH_2)_3COOH \longrightarrow CH_3(CH_2)_3-\overset{O}{\overset{\|}{C}}-OCH_3$ (two ways)

valeric acid — methyl valerate

(f) 

(g) 

(h) 

21-20 Show how you would use extractions with a separatory funnel to separate a mixture of the following compounds: benzoic acid, phenol, benzyl alcohol, aniline.

21-21 When pure (*S*)-lactic acid is esterified by racemic 2-butanol, the product is 2-butyl lactate, with the following structure:

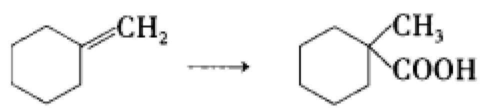
$$\underset{\text{lactic acid}}{CH_3-\overset{OH}{\overset{|}{C}H}-COOH} + \underset{\text{2-butanol}}{CH_3-\overset{OH}{\overset{|}{C}H}-CH_2CH_3} \overset{H^+}{\rightleftharpoons} \underset{\text{2-butyl lactate}}{CH_3-\overset{OH}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}-O-\overset{CH_3}{\overset{|}{C}H}-CH_2CH_3}$$

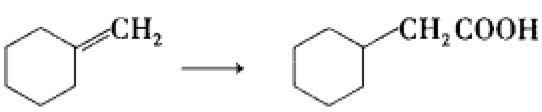
(a) Draw three-dimensional structures of the two stereoisomers formed, specifying the configuration at each asymmetric carbon atom. (Using your models may be helpful.)

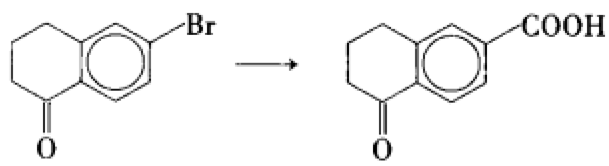
(b) Determine the relationship between the two stereoisomers you have drawn.

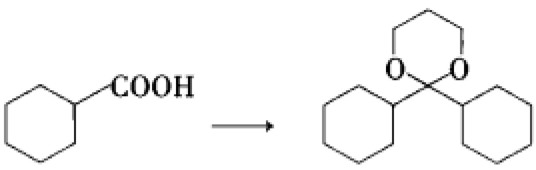
21-22 Show how you would accomplish the following multistep syntheses.

(a) $PhCH_2CH_2OH \longrightarrow PhCH_2CH_2COOH$

(b) 

(c) 

(d) 

(e) 

21-23 In the presence of a trace of acid, δ-hydroxyvaleric acid forms a cyclic ester (lactone).

$$\underset{\delta\text{-hydroxyvaleric acid}}{HO-CH_2CH_2CH_2CH_2-COOH}$$

(a) Give the structure of the lactone, called δ-valerolactone.

(b) Propose a mechanism for the formation of δ-valerolactone.

21-24 We have seen that an acid chloride reacts with an alcohol to form an ester.

$$R-\overset{O}{\overset{\|}{C}}-Cl + R'-OH \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-R' + HCl$$

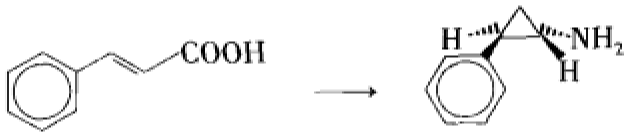
An acid chloride also reacts with another carboxylic acid molecule. The product is an acid anhydride.

$$R-\overset{O}{\overset{\|}{C}}-Cl + R'-\overset{O}{\overset{\|}{C}}-OH \longrightarrow \underset{\text{acid anhydride}}{R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R'} + HCl$$

Propose a mechanism for the reaction of benzoyl chloride (PhCOCl) with acetic acid, and show the structure of the resulting anhydride.

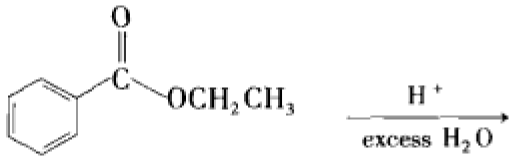
21-25 The antidepressant drug *tranylcypromine* is a primary amine with the amino group on a cyclopropane ring. Show how you would convert *trans*-cinnamic acid to tranylcypromine. (*Hint*: The cyclopropyl group is a poor S_N2 substrate, like a terti-

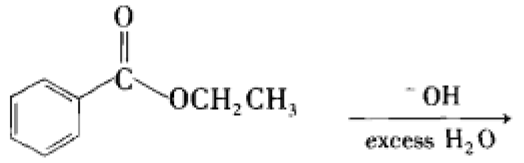
ary group. Consider reactions that can make primary amines with tertiary alkyl groups.)



trans-cinnamic acid → tranylcypromine

21−26 Predict the products and propose mechanisms for the following reactions.

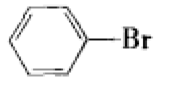
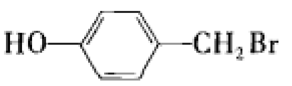
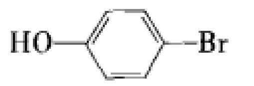
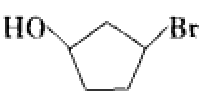
(a) 

(b) 

(c)

(d)

21−27 Two of the methods for converting alkyl halides to carboxylic acids are covered in Sections 21−7A and 21−7B. One is formation of a Grignard reagent followed by addition of carbon dioxide and then dilute acid. The other is substitution by cyanide ion, followed by hydrolysis of the resulting nitrile. For each of the following conversions, decide whether either or both of these methods would work, and explain why. Show the reactions you would use.

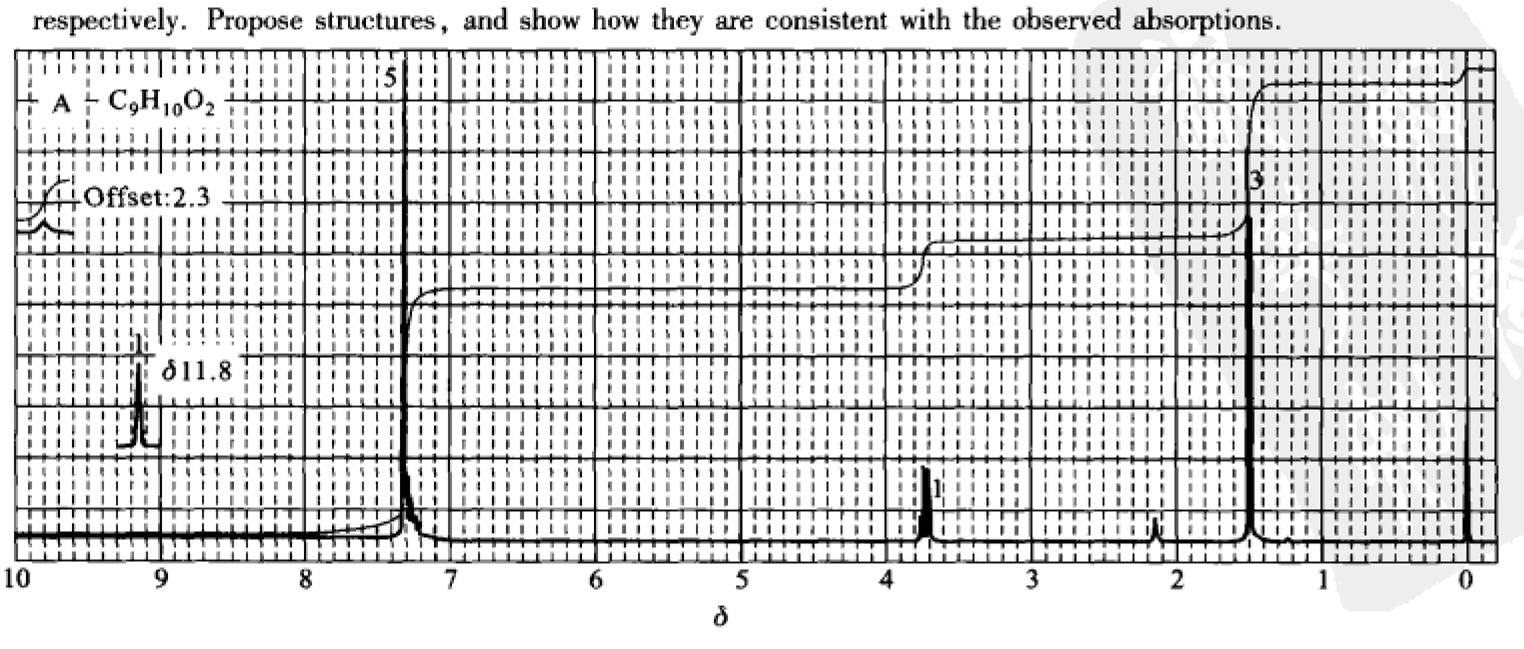
(a)
(b) 
(c) 
(d) 
(e)
(f) 

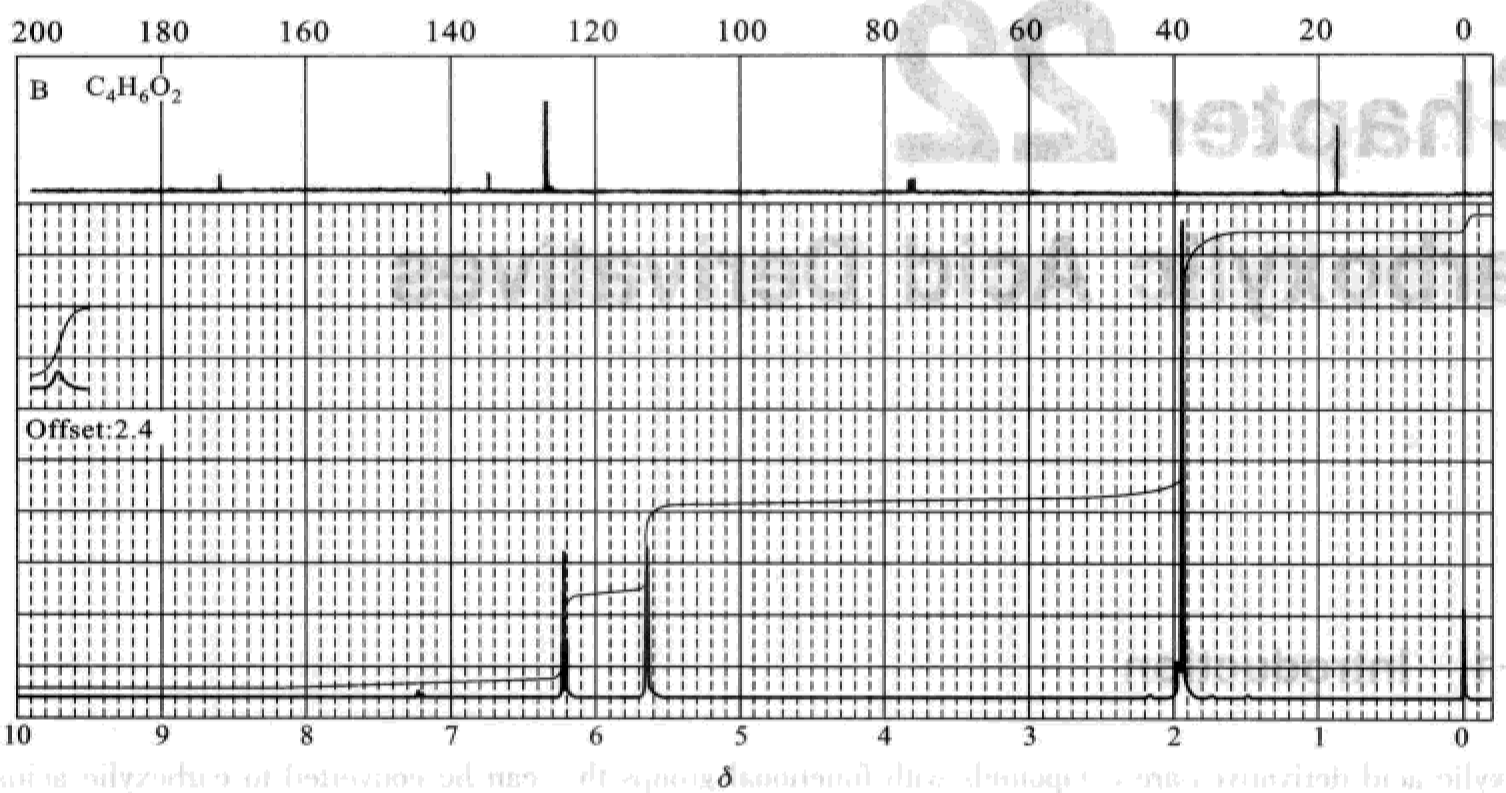
21−28 (a) Hydrogen peroxide (HOOH) has a pK_a of 11.6, making it roughly 10 000 times as strong an acid as water (pK_a = 15.7). Explain why H_2O_2 is a stronger acid than H_2O.

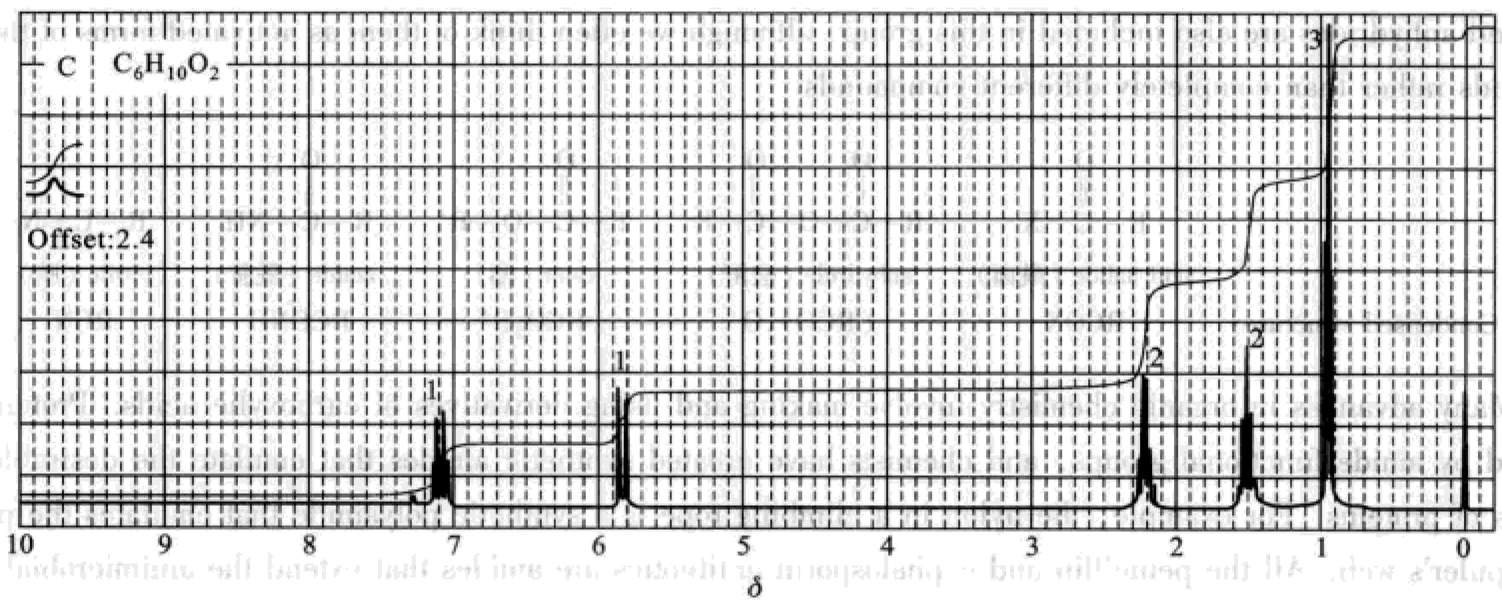
(b) In contrast to part (a), peroxyacetic acid (pK_a = 8.2) is a much *weaker* acid than acetic acid (pK_a = 4.74). Explain why peroxyacetic acid is a weaker acid than acetic acid.

(c) Peroxyacetic acid (bp = 105 ℃) has a lower boiling point than acetic acid (bp = 118 ℃), even though peroxyacetic acid has a higher molecular weight. Explain why peroxyacetic acid is more volatile than acetic acid.

21−29 The following NMR spectra correspond to compounds of formulas (**A**) $C_9H_{10}O_2$, (**B**) $C_4H_6O_2$, and (**C**) $C_6H_{10}O_2$, respectively. Propose structures, and show how they are consistent with the observed absorptions.




B $C_4H_6O_2$
Offset:2.4
δ

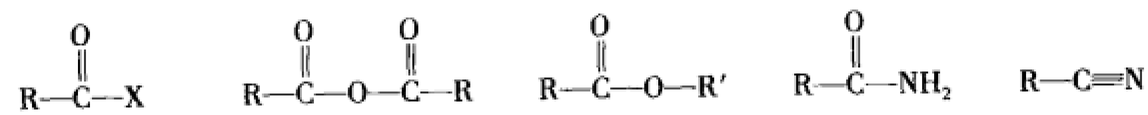

C $C_6H_{10}O_2$
Offset:2.4
δ

Chapter 22

Carboxylic Acid Derivatives

22-1 Introduction

Carboxylic acid derivatives are compounds with functional groups that can be converted to carboxylic acids by a simple acidic or basic hydrolysis. The most important acid derivatives are esters, amides, and nitriles. Acid halides and anhydrides are also included in this group, although we often think of them as activated forms of the parent acids rather than completely different compounds.

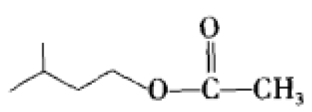


	acid halide（酰卤）	anhydride（酸酐）	ester（酯）	amide（酰胺）	nitrile（腈）
Condensed structure:	RCOX	$(RCO)_2O$	RCO_2R'	$RCONH_2$	RCN

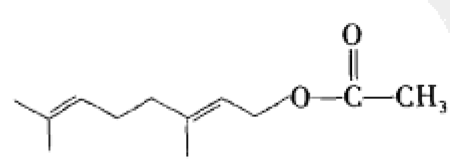
Many advances in organic chemistry involve making and using derivatives of carboxylic acids. Proteins are bonded by amide functional groups, and chemists have created synthetic amides that emulate the desirable properties of proteins. For example, the nylon in a climbing rope is a synthetic polyamide that emulates the protein in a spider's web. All the penicillin and cephalosporin antibiotics are amides that extend the antimicrobial properties of naturally occurring antibiotics.

Like amides, esters are common both in nature and in the chemical industry. Animal fats and vegetable oils are mixtures of esters, as are waxy materials such as beeswax and spermaceti. Plants often synthesize esters that give the characteristic tastes and odors to their fruits and flowers. In addition to making synthetic esters for flavors, odors, and lubricants, chemists have made synthetic polyesters such as Dacron polyester fiber used in clothing and Mylar polyester film used in magnetic recording tapes.

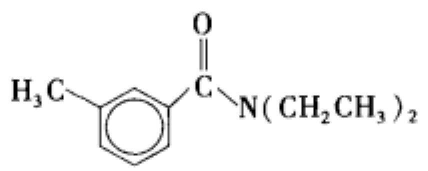
Some examples of naturally occurring esters and amides are shown here. Isoamyl acetate gives ripe bananas their characteristic odor, and geranyl acetate is found in the oil of roses, geraniums, and many other flowers. *N*, *N*-Diethyl-*meta*-toluamide (DEET®) is one of the best insect repellents known, and penicillin G is one of the antibiotics that revolutionized modern medicine.



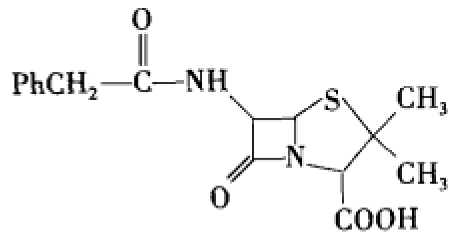
isoamyl acetate [乙酸异戊酯，香蕉油(俗)]
(banana oil)



geranyl acetate [牻牛儿醇乙酸酯，老鹳草油(俗)]
(geranium oil)



N,N-diethyl-*meta*-toluamide
N,N-二乙基间甲基苯甲酰胺



penicillin G (青霉素G,苄青霉素)

22-2 Physical Properties of Carboxylic Acid Derivatives

22-2A Boiling Points and Melting Points

Figure 22-1 is a graph of the boiling points of simple acid derivatives plotted against their molecular weights. The n-alkanes are included for comparison. Notice that esters and acid chlorides have boiling points near those of the unbranched alkanes with similar molecular weights. These acid derivatives contain highly polar carbonyl groups, but the polarity of the carbonyl group has only a small effect on the boiling points.

Examples (MW 55-60)	bp/℃
$CH_3-\overset{\overset{O}{\|}}{C}-NH_2$	222
$CH_3-\overset{\overset{O}{\|}}{C}-OH$	118
$CH_3CH_2CH_2OH$	97
$CH_3CH_2-C{\equiv}N$	97
$H-\overset{\overset{O}{\|}}{C}-OCH_3$	32
$CH_3CH_2CH_2CH_3$	0

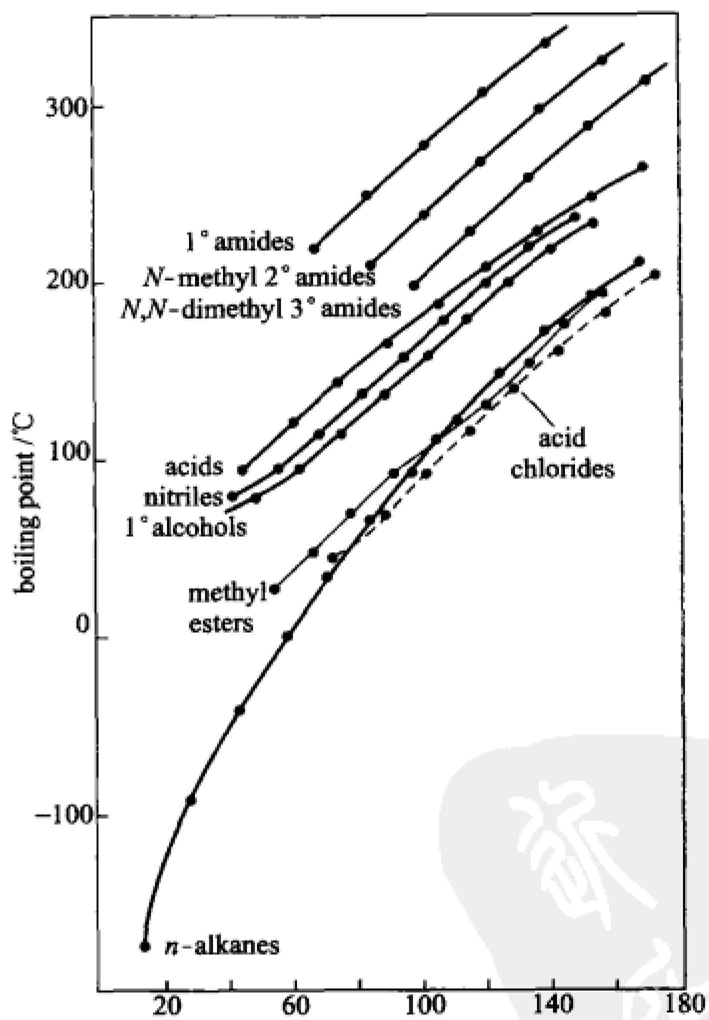
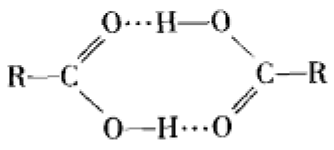


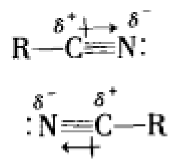
Figure 22-1 Boiling points of acid derivatives plotted against their molecular weights. Alcohols and unbranched alkanes are included for comparison.

Carboxylic acids are strongly hydrogen bonded in the liquid phase, resulting in elevated boiling points. The stable hydrogen-bonded dimer has a higher effective molecular weight and boils at a higher temperature. Nitriles

also have higher boiling points than esters and acid chlorides of similar molecular weight. This effect results from a strong dipolar association between adjacent cyano groups.



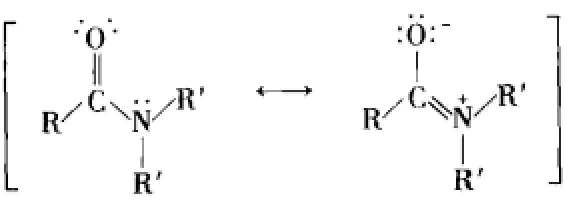
carboxylic acid dimer

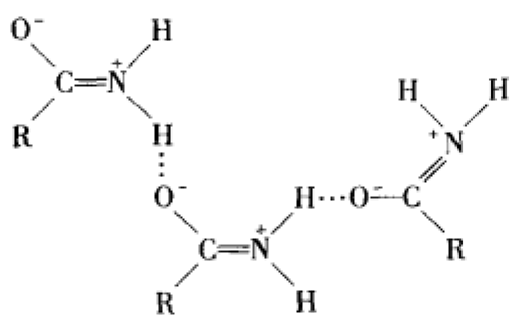


dipolar association of nitriles

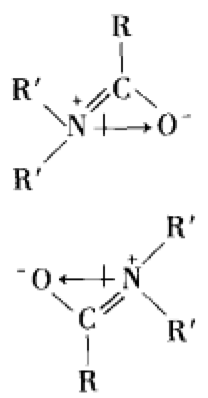
Amides have surprisingly high boiling points and melting points compared with other compounds of similar molecular weight. Primary and secondary amides participate in strong hydrogen bonding, shown in Figure 22−2. The resonance picture shows a partial negative charge on oxygen and a partial positive charge on nitrogen. The positively charged nitrogen polarizes the N—H bond, making the hydrogen strongly electrophilic. The negatively charged oxygen's lone pairs are particularly effective in forming hydrogen bonds to these polarized N—H hydrogens.

Pure tertiary amides lack N—H bonds, so they cannot participate in hydrogen bonding (although they are good hydrogen bond acceptors). Still, they have high boiling points, close to those of carboxy-lic acids of similar molecular weights. Figure 22−2 shows how a pairing of two molecules is strongly attractive, helping to stabilize the liquid phase. Vaporization disrupts this arrangement, so a higher temperature is needed for boiling.





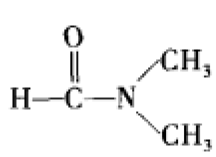
hydrogen bonding



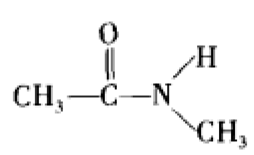
intermolecular attraction

Figure 22−2 The resonance picture of an amide shows its strongly polar nature.

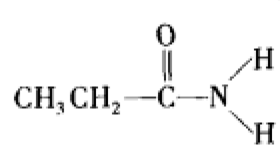
Strong hydrogen bonding between molecules of primary and secondary amides also results in unusually high melting points. For example, *N*-methylacetamide (secondary, one N—H bond) has a melting point of 28 ℃, which is 89° higher than the melting point (−61 ℃) of its isomer dimethylformamide (tertiary, no N—H bond). With two N—H bonds to engage in hydrogen bonding, the primary amide propionamide melts at 79 ℃, about 50° higher than its secondary isomer *N*-methylacetamide.



dimethylformamide
mp −61 ℃



N-methylacetamide
mp 28 ℃



propionamide
mp 79 ℃

22−2B Solubility

Acid derivatives (esters, acid chlorides, anhydrides, nitriles, and amides) are soluble in common organic solvents such as alcohols, ethers, chlorinated alkanes, and aromatic hydrocarbons. Acid chlorides and anhydrides cannot be used in nucleophilic solvents such as water and alcohols, however, because they react with these solvents. Many of the smaller esters, amides, and nitriles are relatively soluble in water (Table 22−1) because of their high polarity and their ability to form hydrogen bonds with water.

TABLE 22−1 Esters, Amides, and Nitriles Commonly Used as Solvents for Organic Reactions

Compound	Name	mp/℃	bp/℃	Water Solubility
$CH_3-C(=O)-OCH_2CH_3$	ethyl acetate (乙酸乙酯)	−83	77	10%
$H-C(=O)-N(CH_3)_2$	dimethylformamide (DMF) (*N,N*-二甲基甲酰胺)	−61	153	miscible
$CH_3-C(=O)-N(CH_3)_2$	dimethylacetamide (DMA) (*N,N*-二甲基乙酰胺)	−20	165	miscible
$CH_3-C\equiv N$	acetonitrile(乙腈)	−45	82	miscible

Esters, tertiary amides, and nitriles are frequently used as solvents for organic reactions because they provide a polar reaction medium without O—H or N—H groups that can donate protons or act as nucleophiles. Ethyl acetate is a moderately polar solvent with a boiling point of 77 ℃, convenient for easy evaporation from a reaction mixture. Acetonitrile, dimethylformamide (DMF), and dimethylacetamide (DMA) are highly polar solvents that solvate ions almost as well as water, but without the reactivity of O—H or N—H groups. These three solvents are miscible with water and are often used as solvent mixtures with water.

22−3 Spectroscopy of Carboxylic Acid Derivatives

22−3A Infrared Spectroscopy

Different types of carbonyl groups give characteristic strong absorptions at different positions in the infrared spectrum. As a result, infrared spectroscopy is often the best method to detect and differentiate these carboxylic acid derivatives. Table 22−2 summarizes the characteristic IR absorptions of carbonyl functional groups. We are using about 1 710 cm^{-1} for simple ketones, aldehydes, and acids as a standard for comparison.

TABLE 22−2 Characteristic Carbonyl IR Stretching Absorptions

Functional Group		Frequency	Comments
ketone	$R-C(=O)-R$	C=O, 1 710 cm^{-1}	lower if conjugated, higher if strained

Continue

Functional Group		Frequency	Comments
acid	R—C(=O)—OH	C=O, 1 710 cm^{-1}	lower if conjugated
		O—H, 2 500 - 3 500 cm^{-1}	broad, on top of C—H stretch
ester	R—C(=O)—O—R′	C=O, 1 735 cm^{-1}	lower if conjugated, higher if strained
amide	R—C(=O)—N(H)—R′	C=O, 1 640 - 1 680 cm^{-1}	
		N—H, 3 200 - 3 500 cm^{-1}	two peaks for R—CO—NH_2, one peak for R—CO—NHR′
acid chloride	R—C(=O)—Cl	C=O, 1 800 cm^{-1}	very high frequency
acid anhydride	R—C(=O)—O—C(=O)—R	C=O, 1 800 and 1 750 cm^{-1}	two peaks
nitrile	R—C≡N	C≡N, 2 200 cm^{-1}	just above 2 200 cm^{-1}

22−3B NMR Spectroscopy

NMR spectroscopy of acid derivatives is complementary to IR spectroscopy. For the most part, IR gives information about the functional groups, and NMR gives information about the alkyl groups. In many cases, the combination of IR and NMR provides enough information to determine the structure.

Proton NMR The proton chemical shifts found in acid derivatives are close to those of similar protons in ketones, aldehydes, alcohols, and amines (Figure 22−3). For example, protons alpha to a carbonyl group absorb between $\delta 2.0$ and $\delta 2.5$, whether the carbonyl group is part of a ketone, aldehyde, acid, ester, or amide. The protons of the alcohol-derived group of an ester or the amine-derived group of an amide give absorptions similar to those in the spectrum of the parent alcohol or amine.

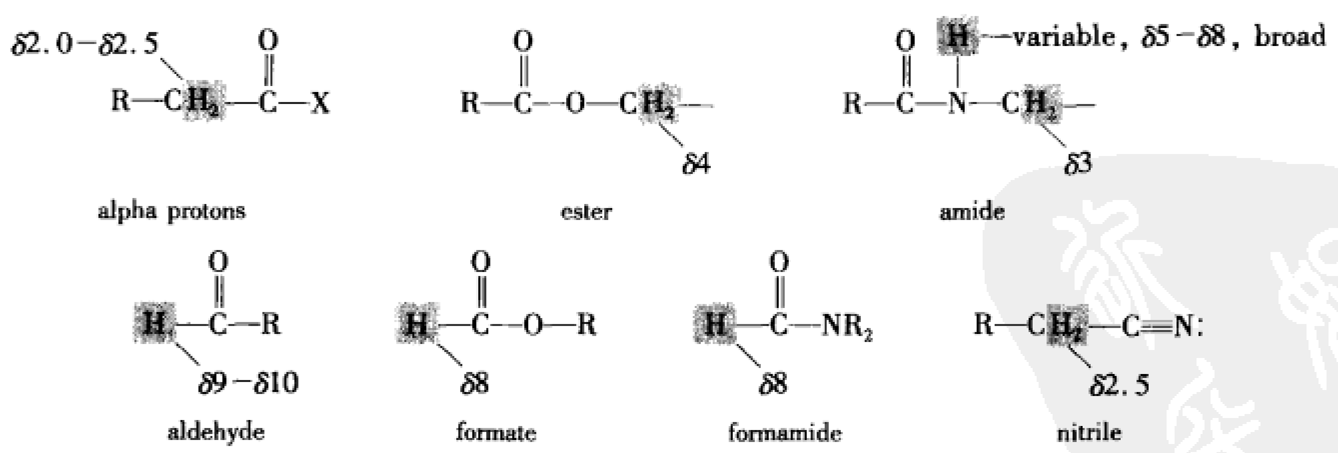
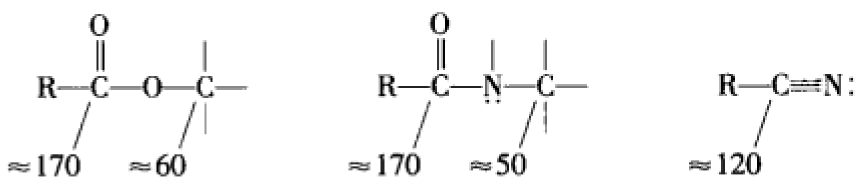


Figure 22−3 Typical absorptions of acid derivatives in the proton NMR spectrum.

Carbon NMR The carbonyl carbons of acid derivatives appear at shifts around 170 to 180, slightly more shielded than the carbonyl carbons of ketones and aldehydes. The α-carbon atoms absorb around 30to 40. The sp^3-hybridized carbons bonded to oxygen in esters absorb around 60 to 80, and those bonded to nitrogen in amides absorb around 40 to 60. The cyano carbon of a nitrile absorbs around 120.



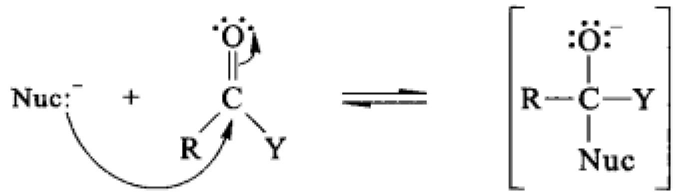
22-4 Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution

Acid derivatives react with a wide variety of nucleophilic reagents under both basic and acidic conditions. Most of these reactions involve **nucleophilic acyl substitutions**, following similar reaction mechanisms. In each case, the nucleophilic reagent adds to the carbonyl group to produce a tetrahedral intermediate, which expels the leaving group to regenerate the carbonyl group. Through this addition-elimination process, the nucleophilic reagent substitutes for the leaving group. In the sections that follow, we consider several examples of these reactions, first under basic conditions and then under acidic conditions. In each case, we will note the similarities with other reactions that follow this same addition-elimination pathway.

Nucleophilic acyl substitutions are also called **acyl transfer** reactions because they transfer the acyl group from the leaving group to the attacking nucleophile. The following is a generalized **addition-elimination mechanism** for nucleophilic acyl substitution under basic conditions.

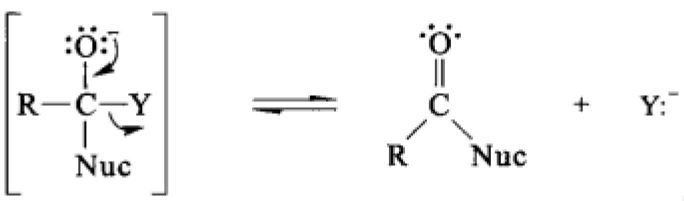
KEY MECHANISM 22-1 Addition-Elimination Mechanism of Nucleophilic Acyl Substitution

***Step 1*:** Addition of the nucleophile gives a tetrahedral intermediate.



nucleophilic attack — tetrahedral intermediate (四面体中间体)

***Step 2*:** Elimination of the leaving group regenerates the carbonyl group.



tetrahedral intermediate — products — leaving group

Depending on the nucleophile and the leaving group, we can imagine converting any acid derivative into almost any other. Not all of these reactions are practical, however. Favorable reactions generally convert a more reactive acid derivative to a less reactive one. Predicting these reactions requires a knowledge of the relative reactivity of acid derivatives.

22-4A Reactivity of Acid Derivatives

Acid derivatives differ greatly in their reactivity toward nucleophilic acyl substitution. For example, water hydrolyzes acetyl chloride in a violently exothermic reaction, while acetamide is stable in boiling water. Acetamide is hydrolyzed only by boiling it in strong acid or base for several hours.

$$CH_3-\overset{O}{\overset{\|}{C}}-Cl + H_2O \xrightarrow{\text{(very fast)}} CH_3-\overset{O}{\overset{\|}{C}}-OH + HCl$$

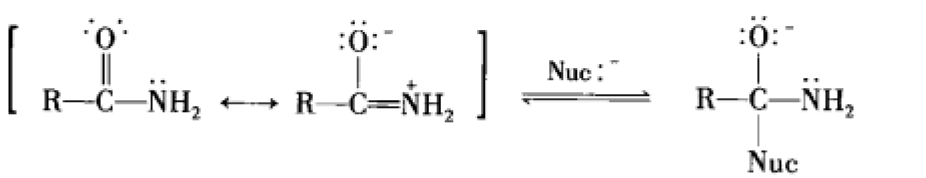
$$CH_3-\overset{O}{\overset{\|}{C}}-NH_2 + Na^{+}\ ^{-}OH \xrightarrow[\text{(slow)}]{H_2O,\ \text{boil}} CH_3-\overset{O}{\overset{\|}{C}}-O^{-}\ ^{+}Na + NH_3$$

The reactivity of acid derivatives toward nucleophilic attack depends on their structure and on the nature of the attacking nucleophile. In general, reactivity follows this order:

Reactivity	*Derivative*		*Leaving group*	*Basicity*
more reactive ↑	acid chloride	$R-\overset{O}{\overset{\|}{C}}-Cl$	Cl^-	less basic ↓
	anhydride	$R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R$	$^{-}O-\overset{O}{\overset{\|}{C}}-R$	
	ester	$R-\overset{O}{\overset{\|}{C}}-O-R'$	$^{-}O-R'$	
	amide	$R-\overset{O}{\overset{\|}{C}}-NH_2$	$^{-}NH_2$	
less reactive	carboxylate	$R-\overset{O}{\overset{\|}{C}}-O^-$	—	more basic

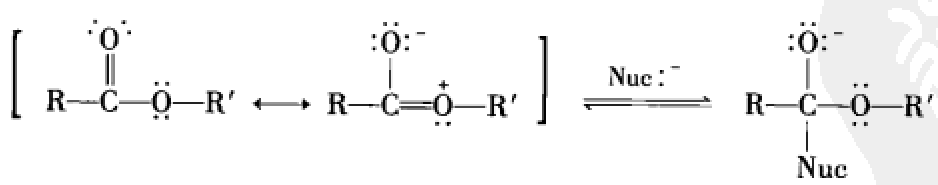
This order of reactivity stems partly from the basicity of the leaving groups. Strong bases are not good leaving groups, and the reactivity of the derivatives decreases as the leaving group becomes more basic.

Resonance stabilization also affects the reactivity of acid derivatives. In amides, for example, resonance stabilization is lost when a nucleophile attacks.



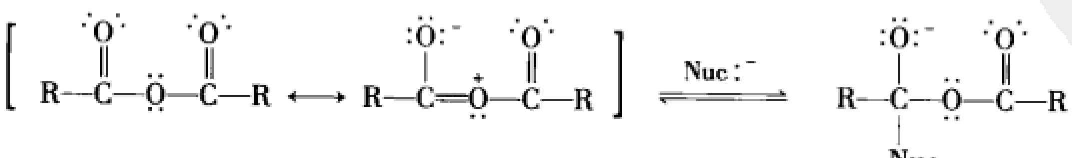
resonance-stabilized no resonance stabilization

A smaller amount of stabilization is present in esters.



weak resonance stabilization no resonance stabilization

Resonance stabilization of an anhydride is like that in an ester, but the stabilization is shared between two carbonyl groups. Each carbonyl group receives less stabilization than an ester carbonyl.



shared, weak resonance stabilization

There is little resonance stabilization of an acid chloride, and it is quite reactive.

In general, we can easily accomplish nucleophilic acyl substitutions that convert more reactive deri-vatives to less reactive ones. Thus, an acid chloride is easily converted to an anhydride, ester, or amide. An anhydride is easily converted to an ester or an amide. An ester is easily converted to an amide, but an amide can be hydrolyzed only to the acid or the carboxylate ion (in basic conditions). Figure 22-4 graphically summarizes these conversions. Notice that thionyl chloride ($SOCl_2$) converts an acid to its most reactive derivative, the acid chloride.

Interconversions of acid derivatives

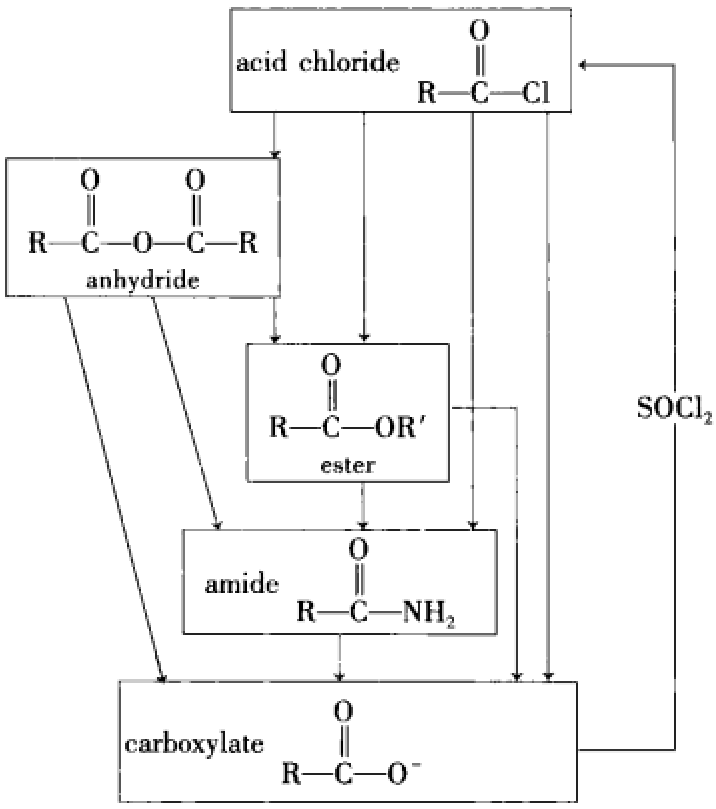


Figure 22-4 More reactive acid derivatives are easily converted to less reactive derivatives.

As we study these conversions of acid derivatives, it may seem that many individual mechanisms are involved. But all these mechanisms are variations on a single theme: the addition-elimination mechanism of nucleophilic acyl substitution. These reactions differ only in the nature of the nucleophile, the leaving group, and proton transfers needed before or after the actual substitution. As we study these mechanisms, watch for these differences and don't feel that you must learn each specific mechanism.

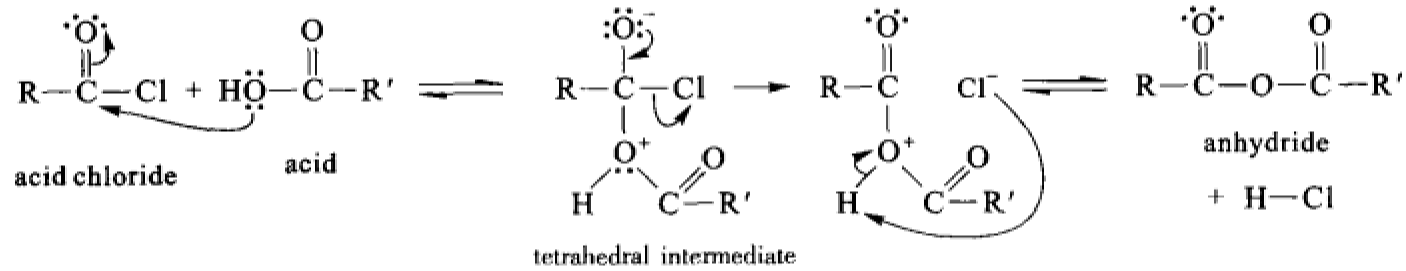
22-4B Favorable Interconversions of Acid Derivatives

Acid chlorides are the most reactive acid derivatives, so they are easily converted to any of the other acid derivatives. Acid chlorides are often used to synthesize anhydrides, esters, and amides. Acid chlorides react with carboxylic acids (or their carboxylate salts) to form anhydrides. Either oxygen atom of the acid can attack the strongly electrophilic carbonyl group of the acid chloride to form a tetrahedral intermediate. Loss of chloride ion and a proton gives the anhydride.

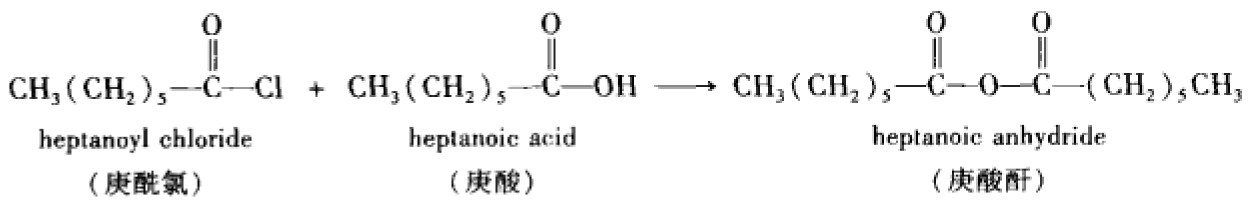
MECHANISM 22-2 Conversion of an Acid Chloride to an Anhydride

This mechanism follows the standard pattern of an addition-elimination mechanism, ending with loss of a proton to give the final product.

***Step 1*: Addition of the nucleophile.** ***Step 2*: Elimination of the leaving group.** ***Step 3*: Loss of a proton.**

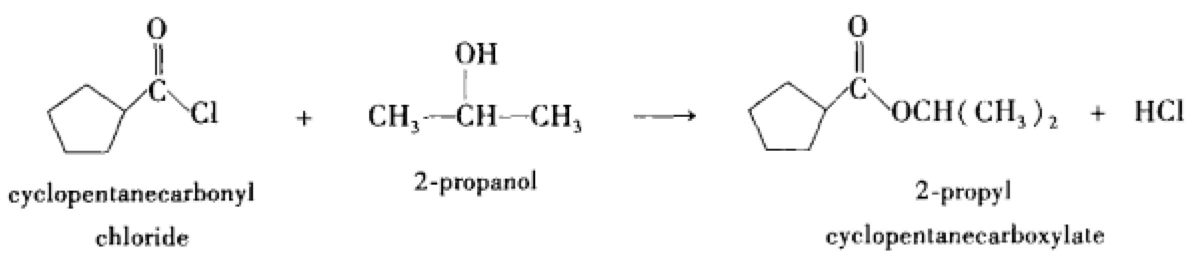


Example

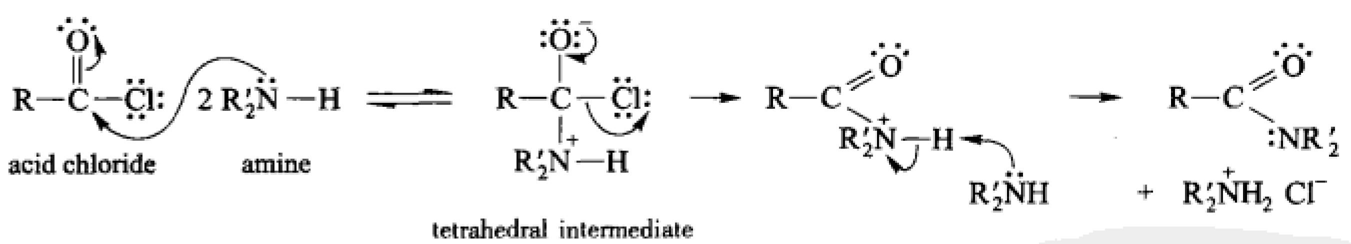


Acid chlorides react rapidly with alcohols to give esters in a strongly exothermic reaction. This reaction requires caution to keep the temperature low to avoid dehydration of the alcohol.

Example

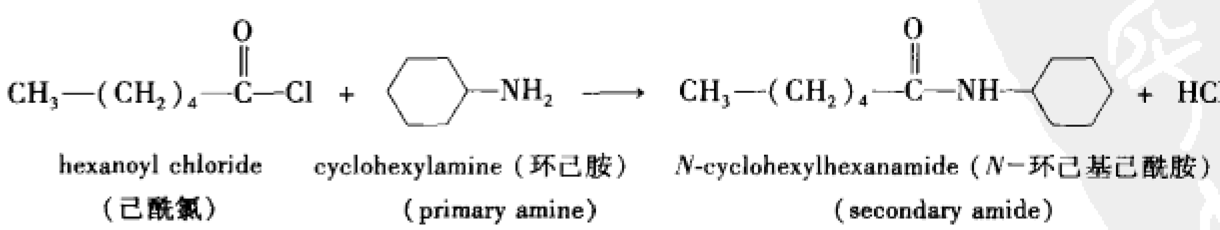


Acid chlorides react rapidly with ammonia and amines to give amides. The HCl generated by the reaction can protonate the amine starting material, so a twofold excess of the amine is required. Alternatively, a base such as pyridine or NaOH may be added with the amine to neutralize the HCl and avoid having to use a large excess of the amine.



Reaction of an acid chloride with ammonia gives a primary amide. With a primary amine, this reaction gives a secondary amide; and with a secondary amine, it gives a tertiary amide.

Example

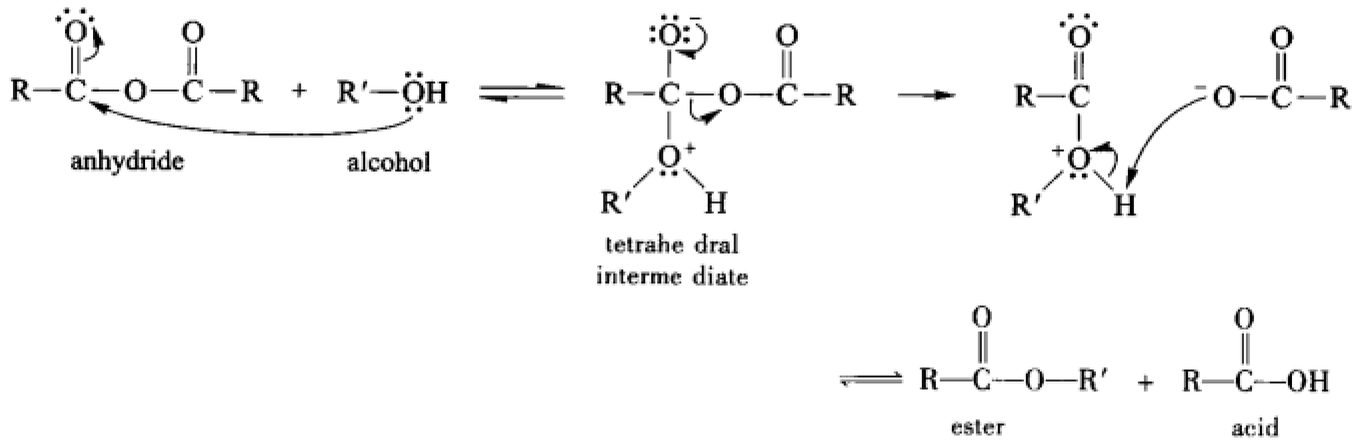


Acid anhydrides are not as reactive as acid chlorides, but they are still activated toward nucleophilic acyl substitution. Reaction with an alcohol gives an ester. Notice that one of the two acid units from the anhydride is expelled as the leaving group.

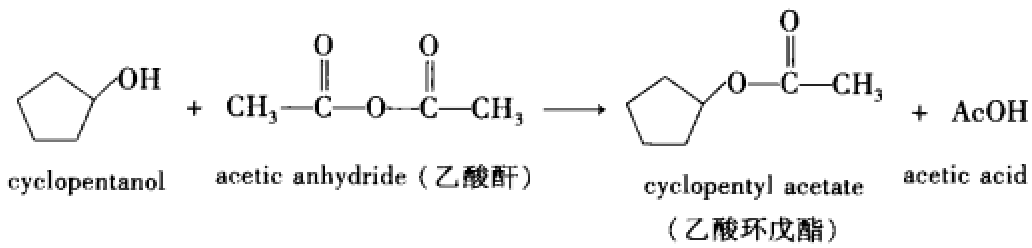
MECHANISM 22-3 Conversion of an Acid Anhydride to an Ester

This reaction follows the standard addition-elimination mechanism, ending with loss of a proton to give the ester.

***Step 1*:** Addition of the nucleophile. ***Step 2*:** Elimination of the leaving group. ***Step 3*:** Loss of a proton.

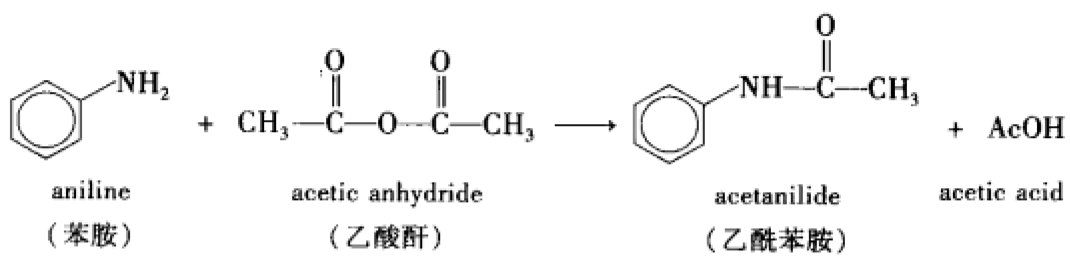


Example



Anhydrides react quickly with ammonia and amines. Reaction of an anhydride with ammonia gives a primary amide. With a primary amine, the reaction gives a secondary amide; and with a secondary amine, it gives a tertiary amide.

Example

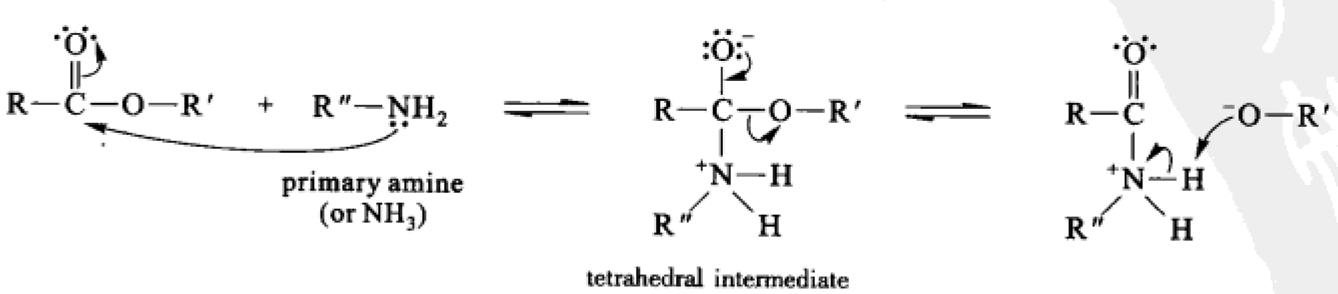


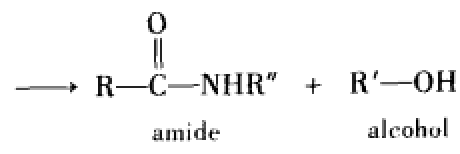
Esters are less reactive than anhydrides, but they can be converted to amides by heating with ammonia or an amine. This reaction is called **ammonolysis**, meaning "lysis (cleavage) by an amine." Ammonolysis using ammonia gives primary amides. Primary amines react to give secondary amides, and secondary amines react (often slowly) to give tertiary amides. In each case, the acyl group of the ester is transferred from the oxygen atom of the alcohol to the nitrogen atom of the amine.

MECHANISM 22-4 Conversion of an Ester to an Amide (Ammonolysis of an Ester)

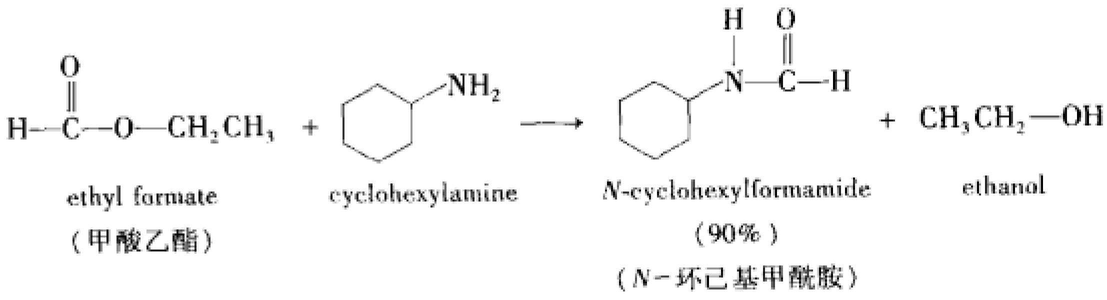
This is yet another standard addition-elimination mechanism, ending with loss of a proton to give the amide.

***Step 1*:** Addition of the nucleophile. ***Step 2*:** Elimination of the leaving group. ***Step 3*:** Loss of a proton.





Example



PROBLEM 22-1

(a) Propose a mechanism for the reaction of benzyl alcohol with acetyl chloride to give benzyl acetate.

(b) Propose a mechanism for the reaction of benzoic acid with acetyl chloride to give acetic benzoic anhydride

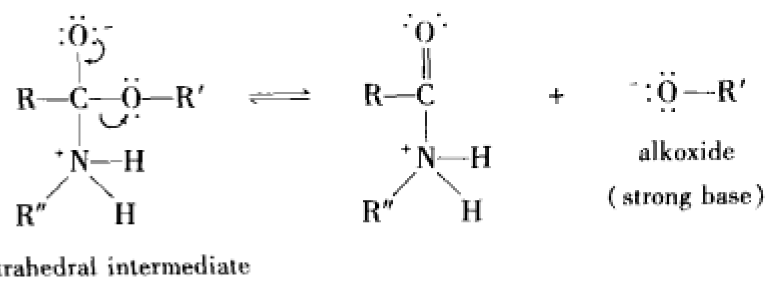
(c) Propose a *second* mechanism for the reaction of benzoic acid with acetyl chloride to give acetic benzoic anhydride. This time, let the *other* oxygen of benzoic acid serve as the nucleophile to attack the carbonyl group of acetyl chloride. Because proton transfers are fast between these oxygen atoms, it is difficult to differentiate between these two mechanisms experimentally.

(d) Propose a mechanism for the reaction of aniline with acetic anhydride to give acetanilide.

(e) Propose a mechanism for the reaction of aniline with ethyl acetate to give acetanilide. What is the leaving group in your proposed mechanism? Would this be a suitable leaving group for an S_N2 reaction?

22-4C Leaving Groups in Nucleophilic Acyl Substitutions

Loss of an alkoxide ion as a leaving group in the second step of the ammonolysis of an ester should surprise you.



In our study of alkyl substitution and elimination reactions (S_N1, S_N2, E1, E2), we saw that strong bases such as hydroxide and alkoxide are poor leaving groups for these reactions. Figure 22-5 compares the acyl addition-elimination mechanism with the S_N2 mechanism. The differences in the mechanisms explain why strong bases may serve as leaving groups in acyl substitution, even though they cannot in alkyl substitution.

The S_N2 reaction's one-step mechanism is not strongly endothermic or exothermic. The bond to the leaving group is about half broken in the transition state, so the reaction rate is sensitive to the nature of the leaving group. With a poor leaving group such as alkoxide, this reaction is quite slow.

In the acyl substitution, the leaving group leaves in a separate second step. This second step is highly exothermic, and the Hammond postulate predicts that the transition state resembles the reactant: the tetrahedral intermediate. In this transition state, the bond to the leaving group has barely begun to break. The energy of the transition state (and therefore the reaction rate) is not very sensitive to the nature of the leaving group.

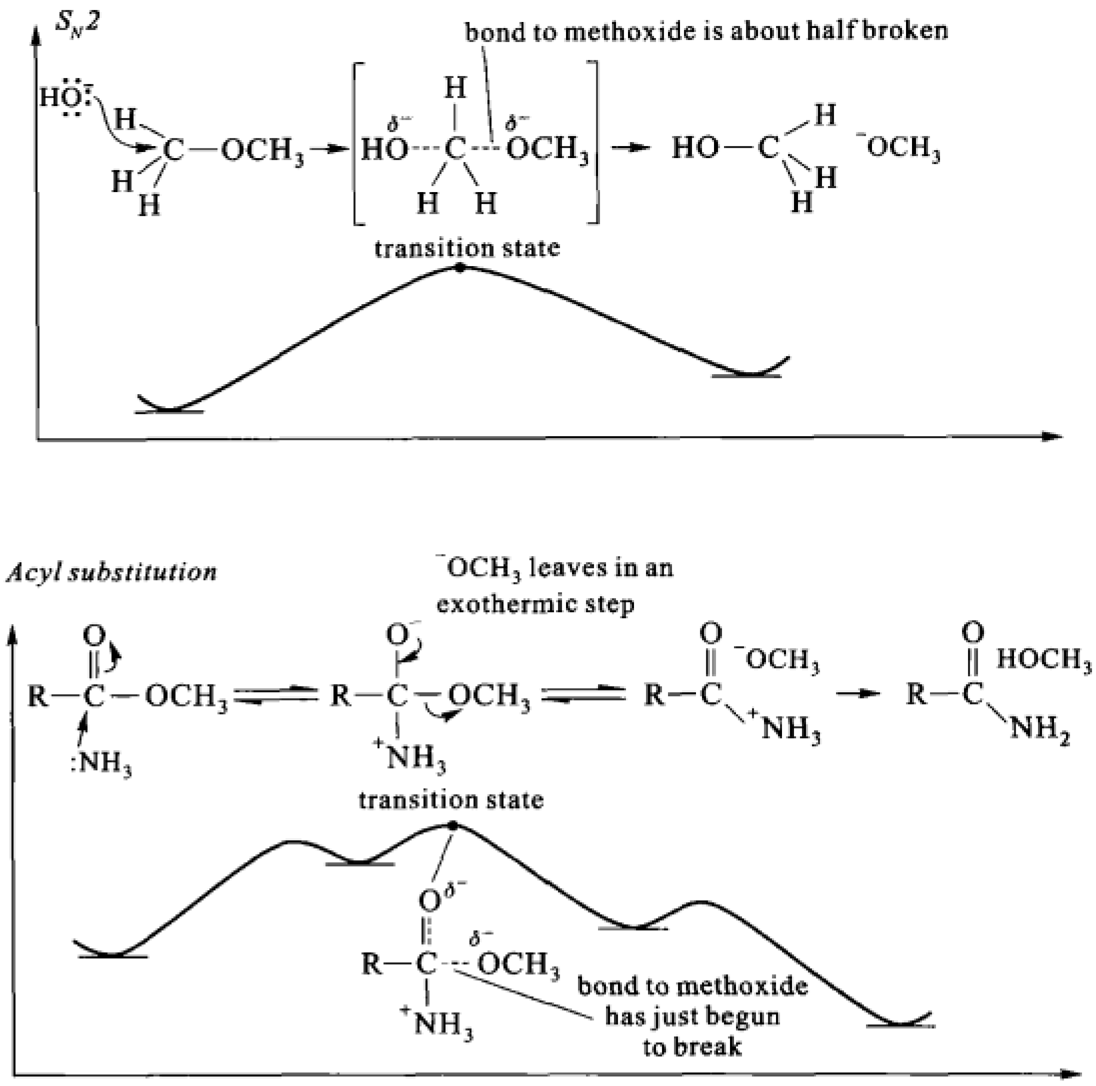


Figure 22-5 Comparison of S_N2 and acyl addition-elimination reactions with methoxide as the leaving group.

Nucleophilic acyl substitution is our first example of a reaction with strong bases as leaving groups. We will see many additional examples of such reactions. In general, a strong base may serve as a leaving group if it leaves in a highly exothermic step, usually converting an unstable, negatively charged intermediate to a stable molecule.

PROBLEM 22-2

Which of the following proposed reactions would take place quickly under mild conditions?

(a) $CH_3C(=O)NH_2 + NaCl \longrightarrow CH_3C(=O)Cl + NaNH_2$

(b) $Ph{-}C(=O){-}Cl + CH_3NH_2 \longrightarrow Ph{-}C(=O){-}NHCH_3 + HCl$

(c) $(CH_3)_2CH{-}C(=O){-}NH_2 + CH_3OH \longrightarrow (CH_3)_2CH{-}C(=O){-}OCH_3 + NH_3$

(d) $CH_3CH_2{-}C(=O){-}Cl + CH_3{-}C(=O){-}OH \longrightarrow CH_3CH_2{-}C(=O){-}O{-}C(=O){-}CH_3 + HCl$

(e) $CH_3{-}C(=O){-}O{-}C(=O){-}CH_3 + CH_3NH_2 \longrightarrow CH_3{-}C(=O){-}NHCH_3 + CH_3COOH$

PROBLEM 22-3

Show how you would synthesize the following esters from appropriate acyl chlorides and alcohols.

(a) ethyl propionate (b) phenyl 3-methylhexanoate

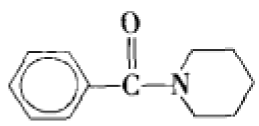
(c) benzyl benzoate (d) cyclopropyl cyclohexanecarboxylate

(e) *t*-butyl acetate (f) diallyl succinate

PROBLEM 22-4

Show how you would use appropriate acyl chlorides and amines to synthesize the following amides.

(a) *N*,*N*-dimethylacetamide (b) acetanilide ($PhNHCOCH_3$)

(c) cyclohexanecarboxamide (d) 

PROBLEM 22-5

(a) Show how you would use acetic anhydride and an appropriate alcohol or amine to synthesize (i) benzyl acetate, (ii) *N*,*N*-diethylacetamide.

(b) Propose a mechanism for each synthesis in part (a).

PROBLEM 22-6

Propose a mechanism for the reaction of benzyl acetate with methylamine. Label the attacking nucleophile and the leaving group, and draw the transition state in which the leaving group leaves.

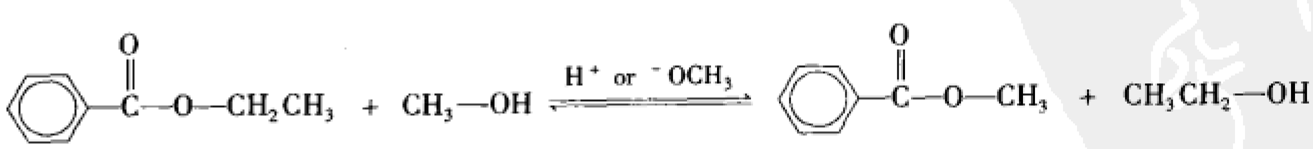
22-5 Transesterification

Esters undergo **transesterification**, in which one alkoxy group substitutes for another, under either acidic or basic conditions. When an ester of one alcohol is treated with a different alcohol in the presence of acid or base, the two alcohol groups can interchange. An equilibrium results, and the equilibrium can be driven toward the desired ester by using a large excess of the desired alcohol or by removing the other alcohol.

Transesterification

$$R-\overset{O}{\overset{\|}{C}}-O-R' + \underset{\text{(large excess)}}{R''-OH} \xrightleftharpoons{H^+ \text{ or } ^-OR''} R-\overset{O}{\overset{\|}{C}}-O-R'' + R'-OH$$

Example



ethyl benzoate (苯甲酸乙酯) methanol methyl benzoate (苯甲酸甲酯) ethanol

Transesterification is possibly the simplest and best example of the acid-catalyzed and base-catalyzed nucleophilic acyl substitution mechanisms because it is an evenly balanced equilibrium with identical mechanisms for the forward and reverse reactions.

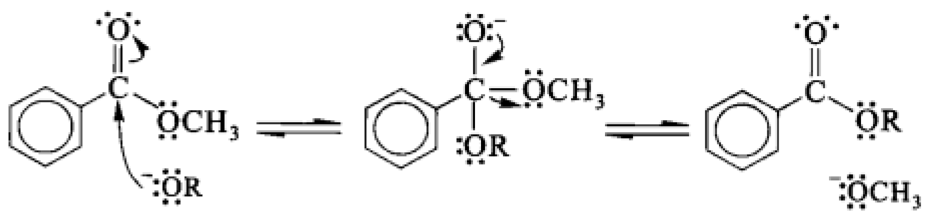
MECHANISM 22-5 Transesterification

Following is a summary of the mechanism of transesterification under basic and acidic conditions.

Base-catalyzed

Base-catalyzed transesterification is a simple two-step nucleophilic acyl substitution:

Step 1: Addition of the nucleophile. ***Step 2***: Elimination of the leaving group.



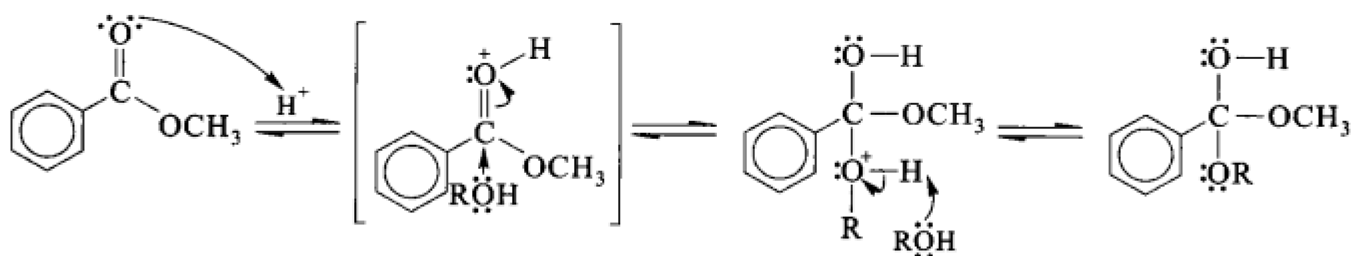
tetrahedral intermediate

Acid-catalyzed

Acid-catalyzed transesterification requires extra proton transfers before and after the major steps. The overall reaction takes place in two stages. The first half of the reaction involves acid-catalyzed addition of the nucleophile, and the second half involves acid-catalyzed elimination of the leaving group.

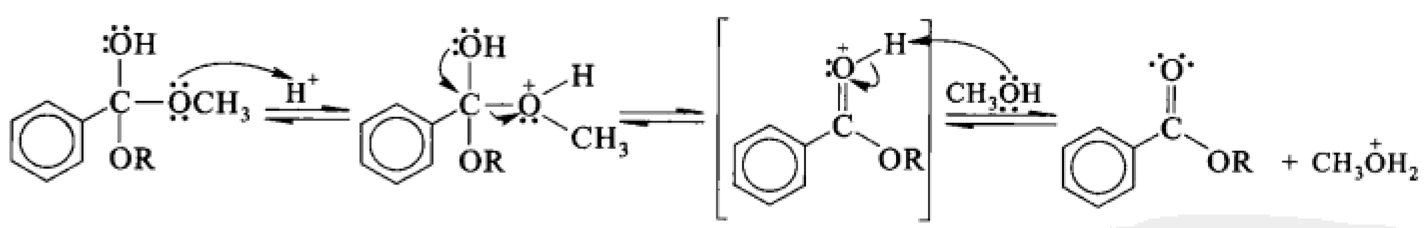
First half: Acid-catalyzed addition of the nucleophile.

Step 1: Protonation of the carbonyl. ***Step 2***: Nucleophile attack. ***Step 3***: Deprotonation.

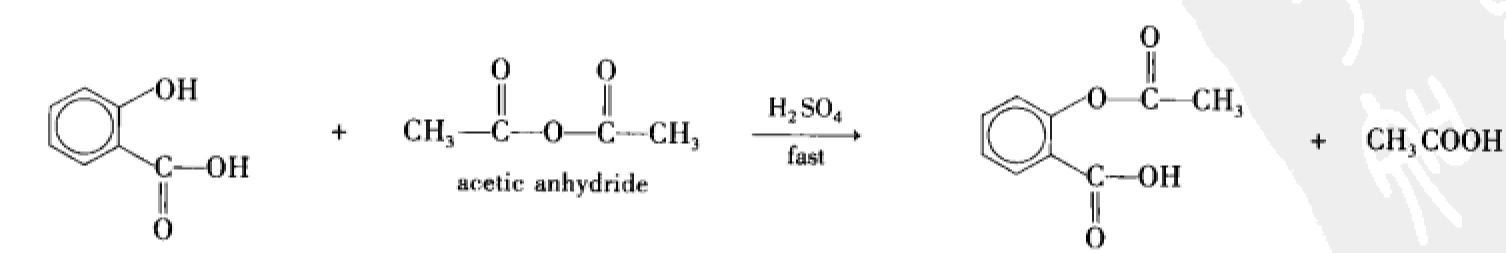


Second half: Acid-catalyzed elimination of the leaving group.

Step 1: Protonation of the leaving group. ***Step 2***: Elimination of the leaving group. ***Step 3***: Deprotonation.



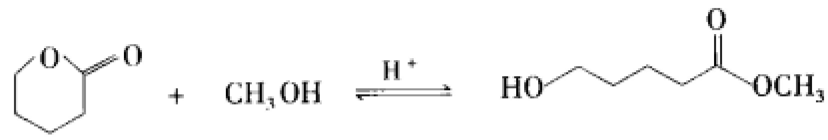
Some reactions that can go as basic nucleophilic acyl substitutions actually work much better with an acid catalyst. For example, aspirin is made from salicylic acid and acetic anhydride. When these reagents are mixed, the reaction goes slowly. Addition of a drop of sulfuric acid accelerates the reaction, and it goes to completion in a minute or two.



salicylic acid (水杨酸) acetic anhydride aspirin (阿司匹林) (acetylsalicylic acid) (乙酰水杨酸)

PROBLEM 22-7

Propose a mechanism for the following ring-opening transesterification.

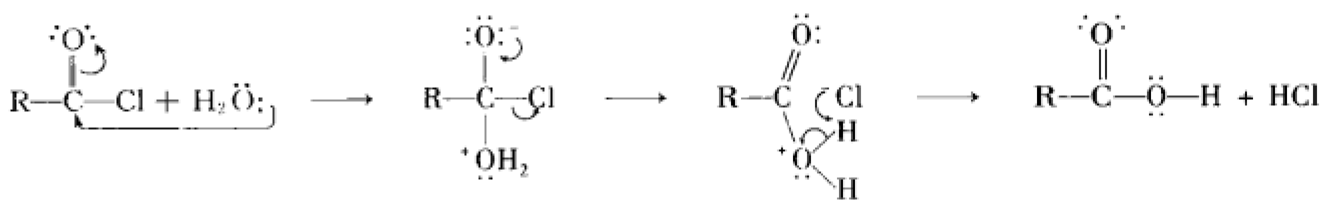


22-6 Hydrolysis of Carboxylic Acid Derivatives

All acid derivatives hydrolyze to give carboxylic acids. In most cases, hydrolysis occurs under either acidic or basic conditions. The reactivity of acid derivatives toward hydrolysis varies from highly reactive acyl halides to relatively unreactive amides.

22-6A Hydrolysis of Acid Halides and Anhydrides

Acid halides and anhydrides are so reactive that they hydrolyze under neutral conditions. Hydrolysis of an acid halide or anhydride is usually an annoying side reaction that takes place on exposure to moist air. Hydrolysis can be avoided by storing acid halides and anhydrides under dry nitrogen and by using dry solvents and reagents.



22-6B Hydrolysis of Esters

Acid-catalyzed hydrolysis of an ester is simply the reverse of the Fischer esterification equilibrium. Addition of excess water drives the equilibrium toward the acid and the alcohol.

Basic hydrolysis of esters, called **saponification**, avoids the equilibrium of the Fischer esterification. Hydroxide ion attacks the carbonyl group to give a tetrahedral intermediate. Expulsion of alkoxide ion gives the acid, and a fast proton transfer gives the carboxylate ion and the alcohol. This strongly exothermic proton transfer drives the saponification to completion. A full mole of base is consumed to deprotonate the acid.

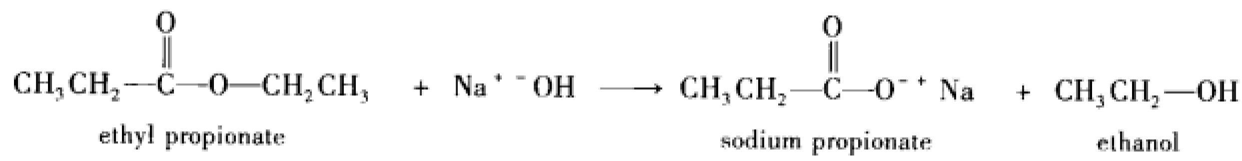
MECHANISM 22-6 Saponification of an Ester

This is another standard addition-elimination mechanism, ending with a proton transfer to give the final products.

Step 1: Addition of the nucleophile. *Step 2*: Elimination of the leaving group. *Step 3*: Proton transfer.

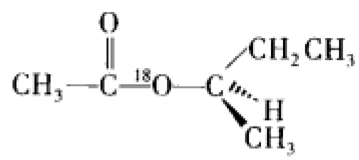
ester — tetrahedral intermediate — acid — alkoxide — carboxylate — alcohol

Example



PROBLEM 22-8

Suppose we have some optically pure (*R*)-2-butyl acetate that has been "labeled" with the heavy ^{18}O isotope at one oxygen atom as shown.



(a) Draw a mechanism for the hydrolysis of this compound under basic conditions. Predict which of the products will contain the ^{18}O label. Also predict whether the 2-butanol product will be pure (*R*), pure (*S*), or racemized.

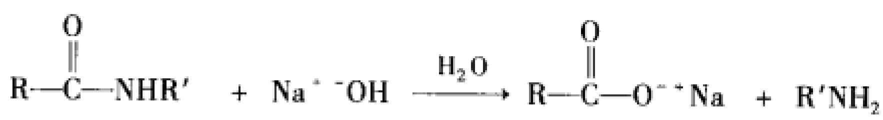
(b) Repeat part (a) for the acid-catalyzed hydrolysis of this compound.

(c) Explain how you would prove experimentally where the ^{18}O label appears in the products. (^{18}O is not radioactive.)

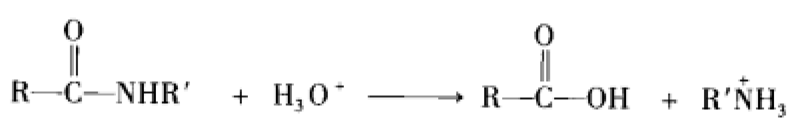
22-6C Hydrolysis of Amides

Amides hydrolyze to carboxylic acids under both acidic and basic conditions. Amides are the most stable acid derivatives, and stronger conditions are required for their hydrolysis than for hydrolysis of an ester. Typical hydrolysis conditions involve prolonged heating in 6 mol/L HCl or 40% aqueous NaOH.

Basic hydrolysis



Acid hydrolysis

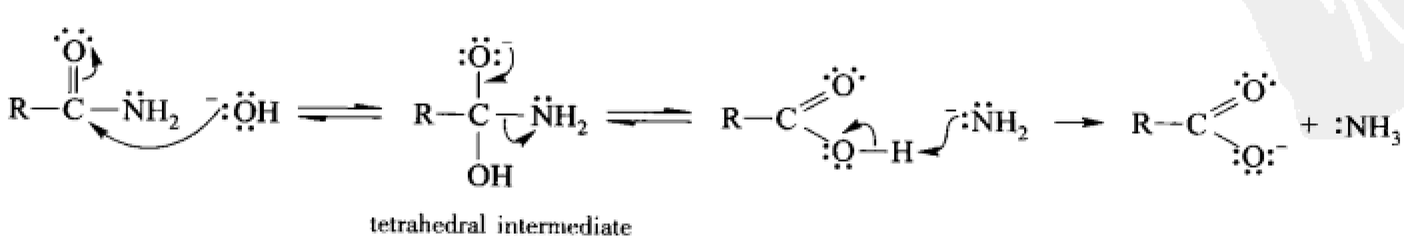


The basic hydrolysis mechanism is similar to that for hydrolysis of an ester. Hydroxide attacks the carbonyl to give a tetrahedral intermediate. Expulsion of an amide ion gives a carboxylic acid, which is quickly deprotonated to give the salt of the acid and ammonia.

MECHANISM 22-7 Basic Hydrolysis of an Amide

This is another standard addition-elimination mechanism, ending with a proton transfer to give the final products.

Step 1: Addition of the nucleophile. ***Step 2***: Elimination of the leaving group. ***Step 3***: Proton transfer.



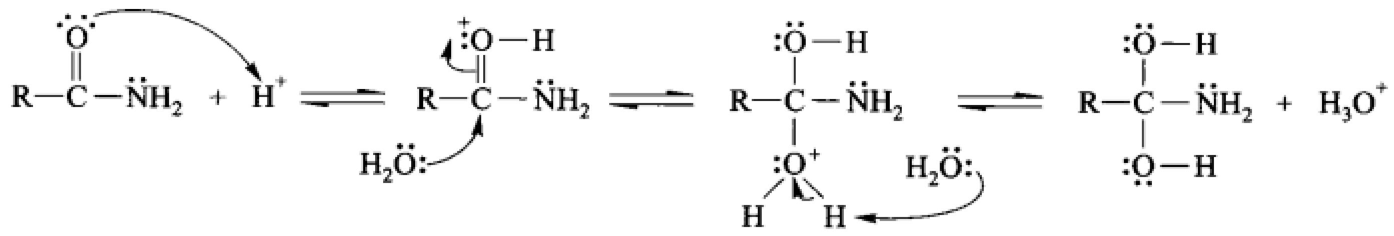
Under acidic conditions, the mechanism of amide hydrolysis resembles the acidcatalyzed hydrolysis of an ester. Protonation of the carbonyl group activates it toward nucleophilic attack by water to give a tetrahedral intermediate. Protonation of the amino group enables it to leave as the amine. A fast exothermic proton transfer gives the acid and the protonated amine.

MECHANISM 22-8 Acidic Hydrolysis of an Amide

This mechanism takes place in two stages.

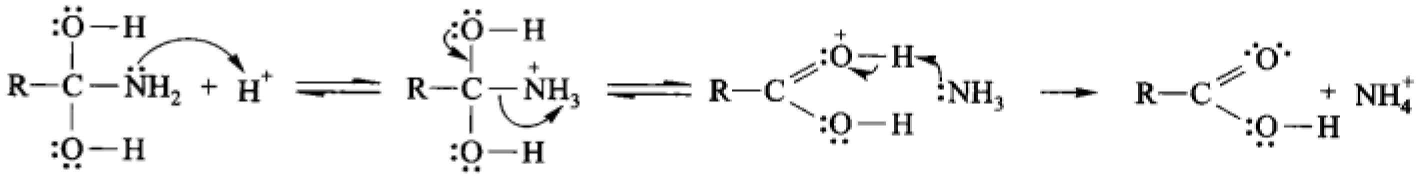
First half: Acid-catalyzed addition of the nucleophile (water).

Step 1: Protonation of the carbonyl ***Step 2***: Addition of the nucleophile ***Step 3***: Loss of a proton



Second half: Acid-catalyzed elimination of the leaving group.

Step 1: Protonation of the leaving group ***Step 2***: Elimination of the leaving group ***Step 3***: Deprotonation



PROBLEM 22-9

Draw the important resonance contributors for both resonance-stabilized cations in the mechanism for acid-catalyzed hydrolysis of an amide.

PROBLEM 22-10

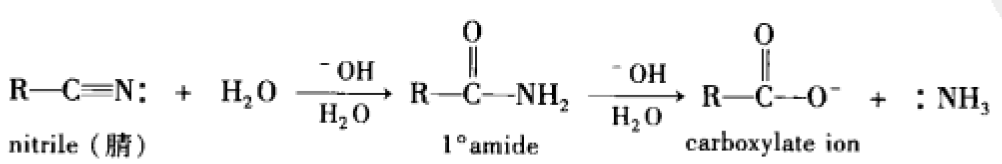
Propose a mechanism for the hydrolysis of *N,N*-dimethylacetamide

(a) under basic conditions **(b)** under acidic conditions

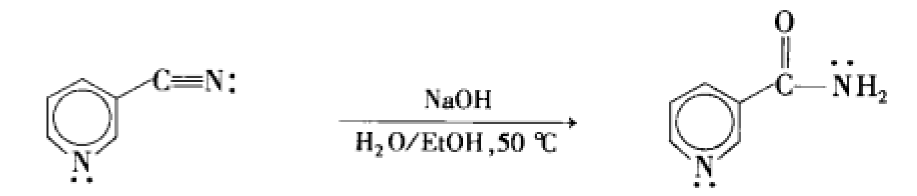
22-6D Hydrolysis of Nitriles

Nitriles are hydrolyzed to amides, and further to carboxylic acids, by heating with aqueous acid or base. Mild conditions can hydrolyze a nitrile only as far as the amide. Stronger conditions can hydrolyze it all the way to the carboxylic acid.

Basic hydrolysis of nitriles



Example



nicotinonitrile（烟腈） nicotinamide（烟酰胺）

Acidic hydrolysis of nitriles

$$\underset{\text{nitrile}}{R-C\equiv N:} \xrightarrow[H_2O]{H^+} \underset{\text{primary amide}}{R-\overset{\overset{O}{\|}}{C}-NH_2} \xrightarrow[H_2O]{H^+} \underset{\text{carboxylic acid}}{R-\overset{\overset{O}{\|}}{C}-OH} + NH_4^+$$

Example

$$\underset{\text{phenylacetonitrile}}{Ph-CH_2-C\equiv N:} \xrightarrow[H_2O/EtOH]{H_2SO_4,\ heat} \underset{\text{phenylacetic acid}}{Ph-CH_3-\overset{\overset{O}{\|}}{C}-OH}$$

22-7 Reduction of Acid Derivatives

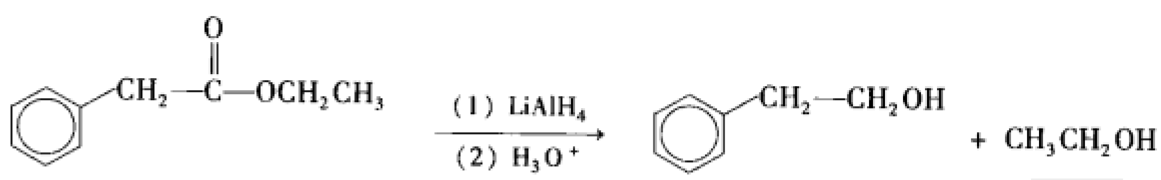
Carboxylic acids and their derivatives can be reduced to alcohols, aldehydes, and amines. Because they are relatively difficult to reduce, acid derivatives generally require a strong reducing agent such as lithium aluminum hydride ($LiAlH_4$).

22-7A Reduction to Alcohols

Lithium aluminum hydride reduces acids, acid chlorides, and esters to primary alcohols.

$$\underset{\substack{\text{ester}\\ \text{(or acid chloride)}}}{R-\overset{\overset{O}{\|}}{C}-O-R'} \xrightarrow{LiAlH_4} \underset{\text{primary alkoxide}}{R-CH_2O^-\ Li^+ + R'-O^-\ Li^+} \xrightarrow{H_3O^+} \underset{\text{primary alcohol}}{R-CH_2OH + R'-OH}$$

Example



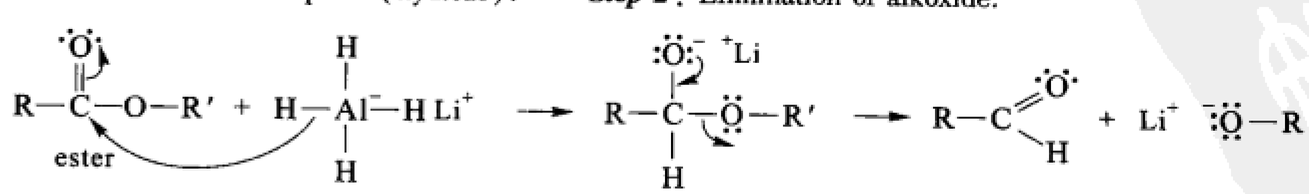
ethyl phenylacetate 2-phenylethanol

Both esters and acid chlorides react through an addition-elimination mechanism to give aldehydes, which quickly reduce to alkoxides. After the reduction is complete, dilute acid is added to protonate the alkoxide.

MECHANISM 22-9 Hydride Reduction of an Ester

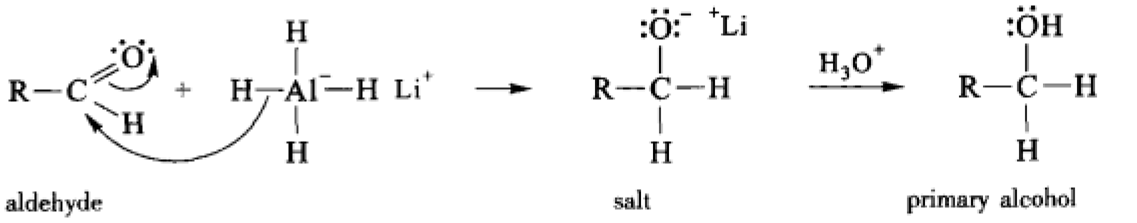
Nucleophilic acyl substitution gives an aldehyde, which reduces further to an alcohol.

Step 1: Addition of the nucleophile (hydride). ***Step 2***: Elimination of alkoxide.



tetrahedral intermediate aldehyde alkoxide

Step 3**:** Addition of a second hydride ion. ***Step 4*****:** Add acid in the workup to protonate the alkoxide.



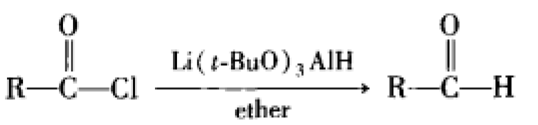
PROBLEM 22-11

(a) In which step(s) of the hydride reduction of an ester does the compound undergo reduction?
(*Hint*: Count the bonds to oxygen.)

(b) Propose a mechanism for the reduction of octanoyl chloride by lithium aluminum hydride.

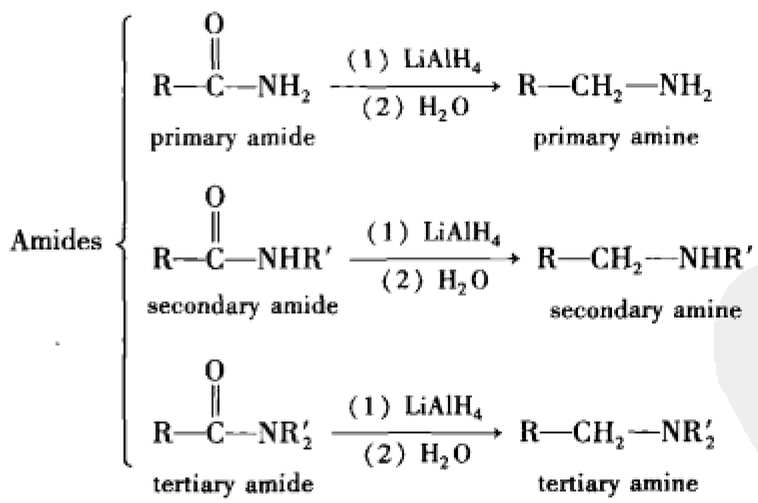
22-7B Reduction to Aldehydes

Acid chlorides are more reactive than other acid derivatives, and they are reduced to aldehydes by mild reducing agents such as lithium aluminum tri (*t*-butoxy) hydride.
This reduction was covered in section 19-6D.

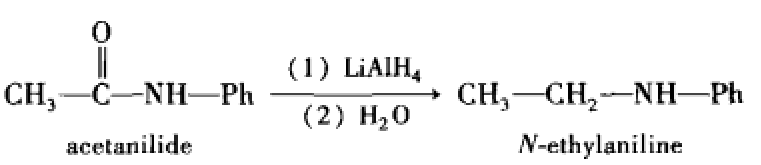


22-7C Reduction to Amines

Lithium aluminum hydride reduces amides and nitriles to amines, providing some of the best synthetic routes to amines. Primary amides and nitriles are reduced to primary amines. Secondary amides are reduced to secondary amines, and tertiary amides are reduced to tertiary amines.



Example

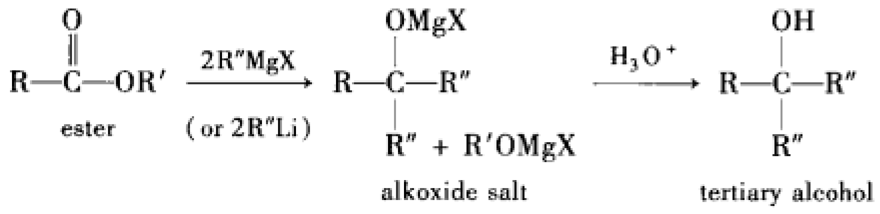


Nitriles are reduced to primary amines.

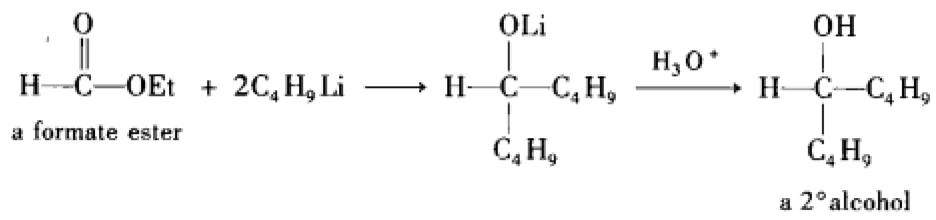
$$R-C\equiv N: \xrightarrow[\text{or (1) LiAlH}_4;\ (2)\ H_2O]{H_2/Pt} R-CH_2-NH_2$$

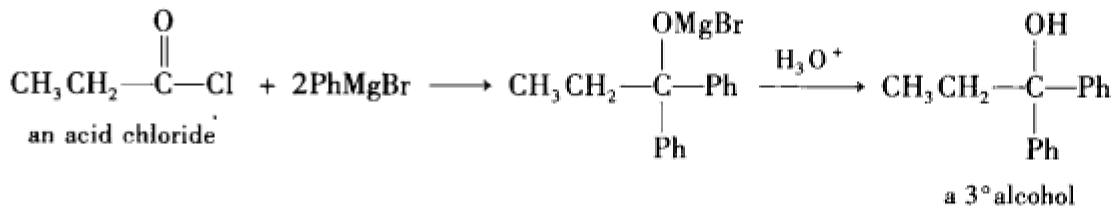
22-8 Reactions of Acid Derivatives with Organometallic Reagents

Esters and Acid Chlorides Grignard and organolithium reagents add twice to acid chlorides and esters to give alkoxides. Protonation of the alkoxides gives alcohols.



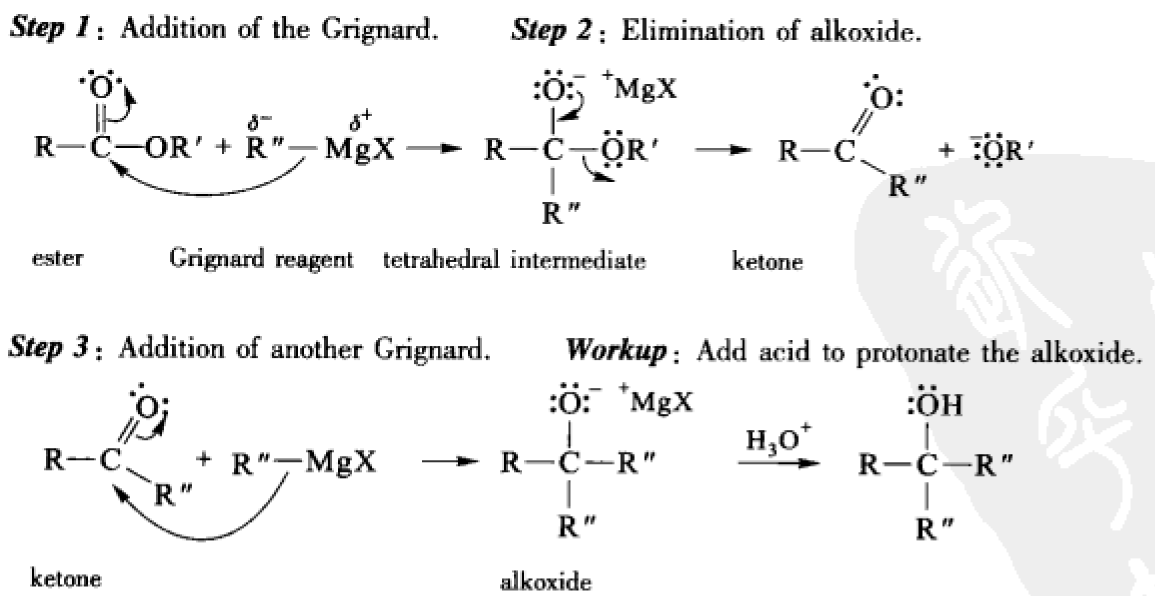
Examples





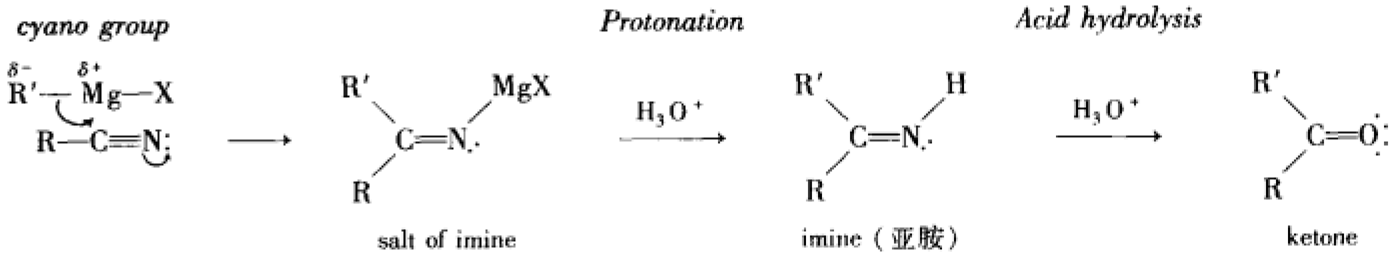
The mechanism involves nucleophilic substitution at the acyl carbon atom. Attack by the carbanion-like organometallic reagent, followed by elimination of alkoxide (from an ester) or chloride (from an acid chloride), gives a ketone. A second equivalent of the organometallic reagent adds to the ketone to give the alkoxide. Hydrolysis gives tertiary alcohols, unless the original ester is a formate (R=H), which gives a secondary alcohol. In each case, two of the groups on the product are the same, derived from the organometallic reagent.

MECHANISM 22-10 Reaction of an Ester with 2 mol of a Grignard Reagent

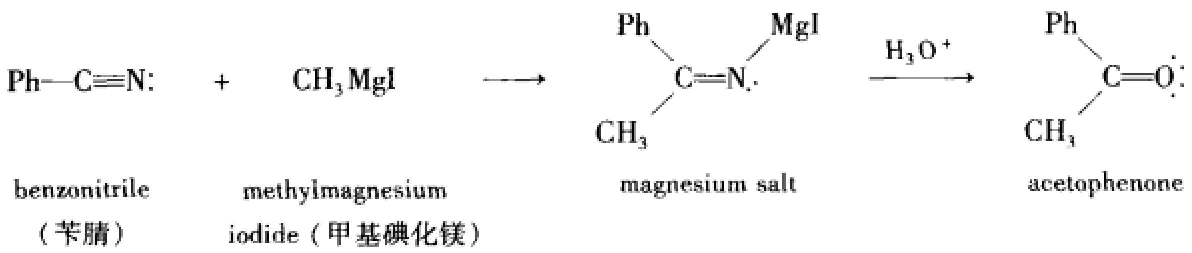


Nitriles A Grignard or organolithium reagent attacks the electrophilic cyano group to form the salt of an imine. Acidic hydrolysis of the salt (in a separate step) gives the imine, which is further hydrolyzed to a ketone.

Attack on the electrophilic cyano group



Example



PROBLEM 22-12

Draw a mechanism for the reaction of propanoyl chloride with 2 mol of phenylmagnesium bromide.

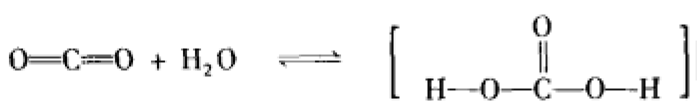
PROBLEM 22-13

Show how you would add a Grignard reagent to an ester or a nitrile to synthesize

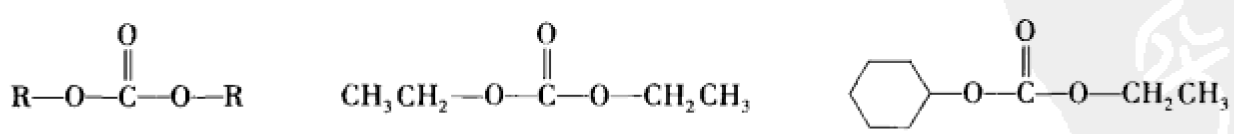
(a) 4-phenyl-4-heptanol (b) 4-heptanol (c) 2-pentanone

22-9 Esters and Amides of Carbonic Acid

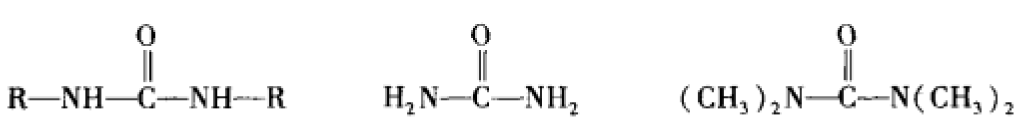
Carbonic acid (H_2CO_3) is formed when carbon dioxide dissolves in water. Although carbonic acid itself is always in equilibrium with carbon dioxide and water, it has several important stable derivatives. **Carbonate esters** are diesters of carbonic acid, with two alkoxy groups replacing the hydroxyl groups of carbonic acid. **Ureas** are diamides of carbonic acid, with two nitrogen atoms bonded to the carbonyl group. The unsubstituted urea, simply called *urea*, is the waste product excreted by mammals from the metabolism of excess protein. **Carbamate esters** (**urethanes**) are the stable esters of the unstable **carbanmic acid**, the monoamide of carbonic acid.



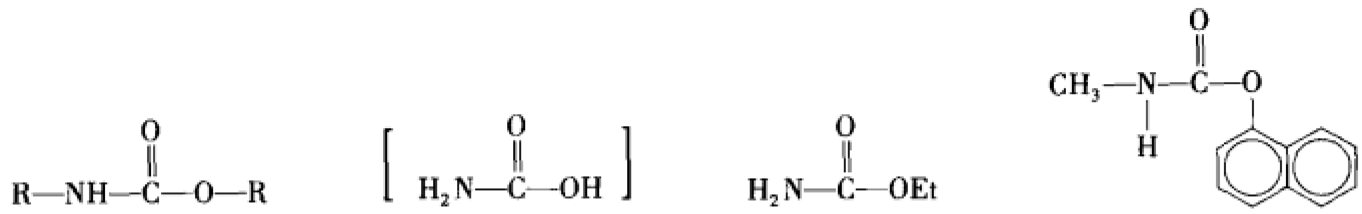
carbonic acid (unstable)（碳酸）



a carbonate ester（碳酸酯） diethyl carbonate（碳酸二乙酯） cyclohexyl ethyl carbonate（碳酸乙基环己基酯）

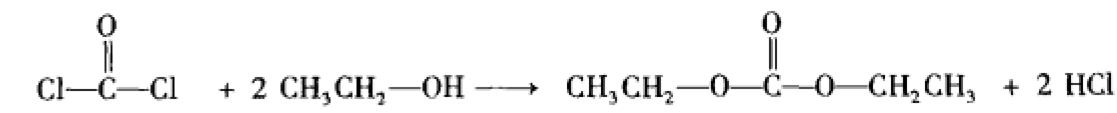


a substituted urea urea（尿素） tetramethylurea（四甲基尿素）

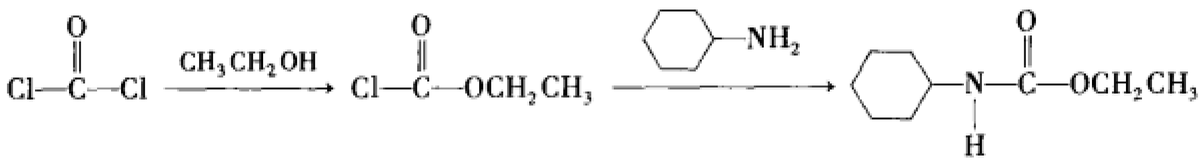


a carbamate or urethane (氨基甲酸酯或尿烷) | carbamic acid (氨基甲酸) (unstable) | ethyl carbamate (氨基甲酸乙酯) | 1-naphthyl-*N*-methylcarbamate (*N*-甲基氨基甲酸-1-萘酯) (Sevin® insecticide)

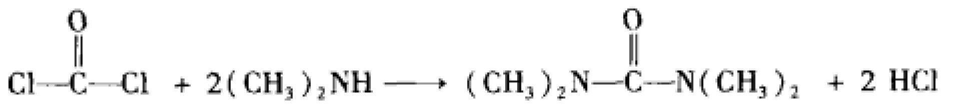
Most of these derivatives are synthesized by nucleophilic acyl substitution from phosgene, the acid chloride of carbonic acid.



phosgene (光气) diethyl carbonate

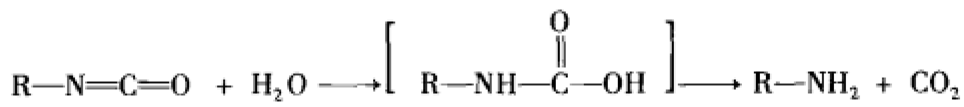


ethyl *N*-cyclohexyl carbamate (*N*-环己基氨基甲酸乙酯)

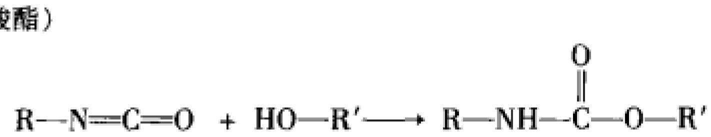


tetramethylurea

Another way of making urethanes is to treat an alcohol or a phenol with an **isocyanate**, which is an anhydride of a carbamic acid. Although the carbamic acid is unstable, the urethane is stable. This is the way Sevin® insecticide is made.

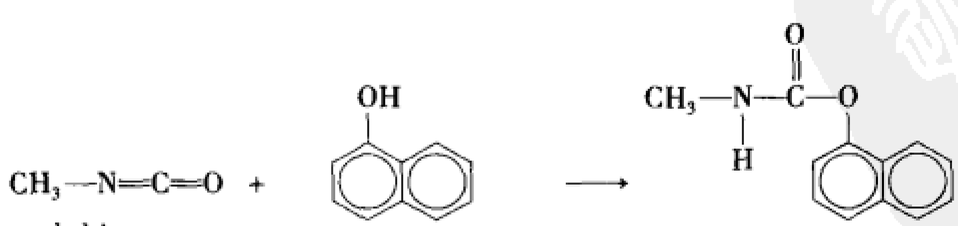


an isocyanate (异氰酸酯) a carbamic acid an amine



an isocyanate alcohol a carbamate ester (urethane)

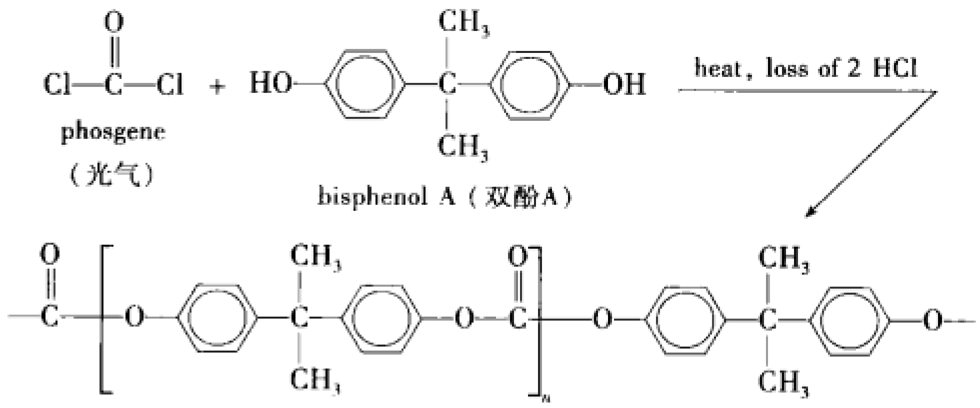
Example



methyl isocyanate (异氰酸甲酯) 1-naphthol (1-萘酚) Sevin® insecticide (杀虫剂)

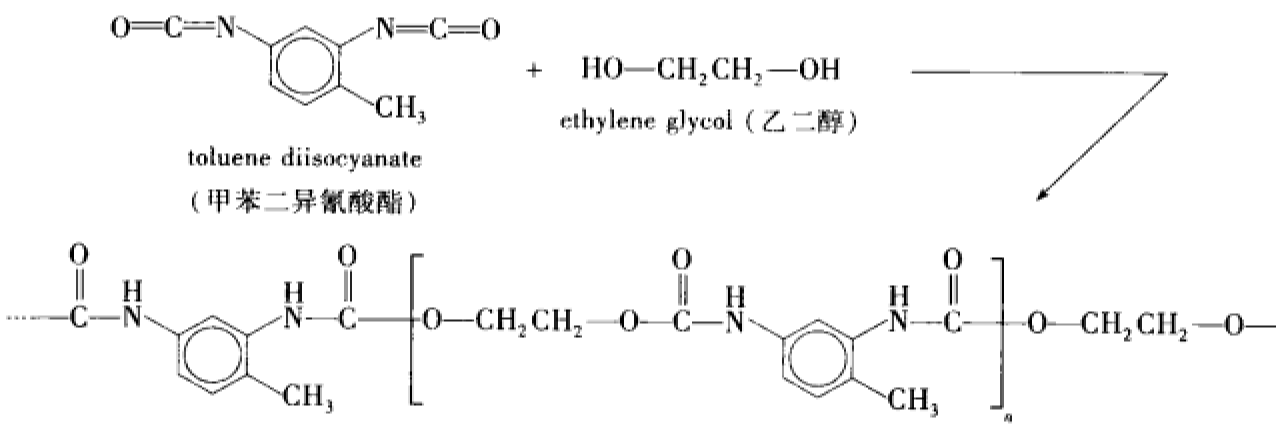
Polycarbonates and Polyurethanes The chemistry of carbonic acid derivatives is particularly important because two large classes of polymers are bonded by linkages containing these functional groups: the **polycarbonates** and the **Polyurethanes**. Polycarbonates are polymers bonded by the carbonate ester linkage, and polyurethanes are polymers bonded by the carbamate ester linkage. Lexan® polycarbonate is a strong, clear polymer

used in bulletproof windows and crash helmets. The diol used to make Lexan® is a phenol called *bisphenol* A, a common intermediate in polyester and polyurethane synthesis.



Lexan® polycarbonate (聚碳酸酯)

A polyurethane results when a diol reacts with a diisocyanate, a compound with two isocyanate groups. A common form of polyurethane is made by the reaction of ethylene glycol with *toluene diisocyanate*.



a polyurethane (聚氨基甲酸酯)

Summary in Chinese

本 章 概 要

一、羧酸衍生物的结构

羧酸衍生物的结构可以用通式表示为：$RC(=O)—Y$、$Y=X$、$—OR'$、$—OC(=O)—R'$、$—NH_2$（或$—NHR'$，$—NR'_2$），分别称为酰卤、酯、酸酐和酰胺，统称为羧酸衍生物。其结构中都含有羰基，羰基碳原子为 sp^2 杂化，平面构型，与羰基直接相连的原子上都有未共用电子对（N、O、X），这一电子对与羰基的 π 键构成 $p-\pi$ 共轭体系，但共轭程度不同，反应活性也不同。

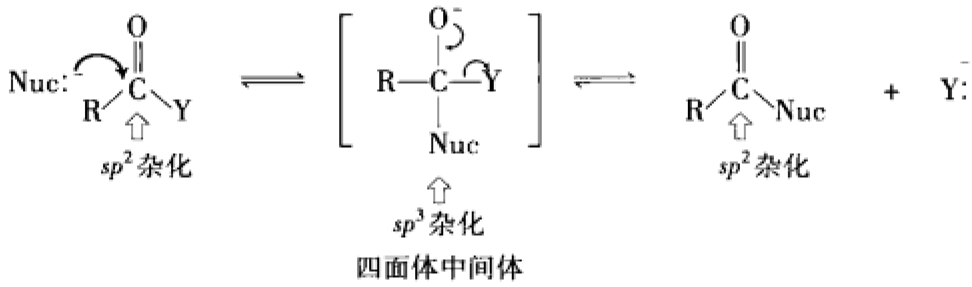
二、羧酸衍生物的物理性质

酰卤、酸酐和酯的沸点较相对分子质量相近的羧酸低，而与相对分子质量相近的酮、醛的沸点相近。酰胺分子间有氢键，其沸点和熔点都比相应的羧酸高。相对分子质量相同的酰胺中，分子中 N—H 键越多，熔、沸点越高，如以下物质溶、沸点高低顺序为：

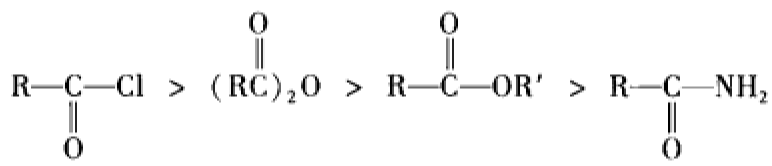
$$CH_3CH_2C(=O)—NH_2 > CH_3C(=O)—NHCH_3 > HC(=O)—N(CH_3)_2$$

三、羧酸衍生物的化学性质

1. 亲核加成-消除反应机理：羧酸衍生物可与水、醇、胺、有机金属化合物反应，反应的实质是亲核试剂进攻羰基碳，发生亲核加成反应，形成一个四面体结构的负离子中间体，中心碳原子由 sp^2 杂化转化为 sp^3 杂化，$p-\pi$ 共轭体系被破坏，而后 Y 以 Y^- 的形式离去（消除），中心碳原子又变成 sp^2 杂化，恢复 $p-\pi$ 共轭体系，生成取代产物。

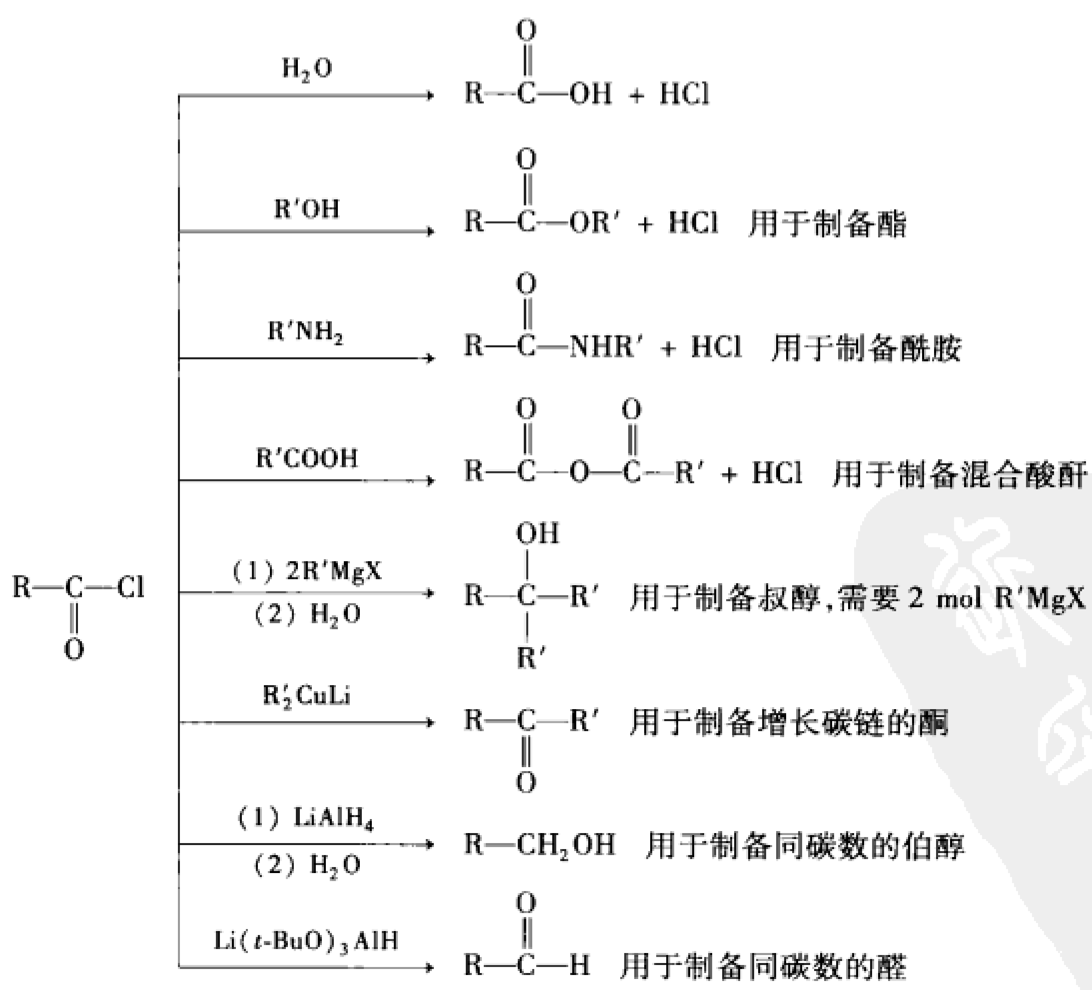


2. 羧酸衍生物的亲核加成反应：羧酸衍生物可以与水反应生成羧酸，与醇反应生成酯，与胺反应生成酰胺，与金属化合物反应生成酮、醇等。反应机理为亲核加成-消除反应。反应活性顺序为：

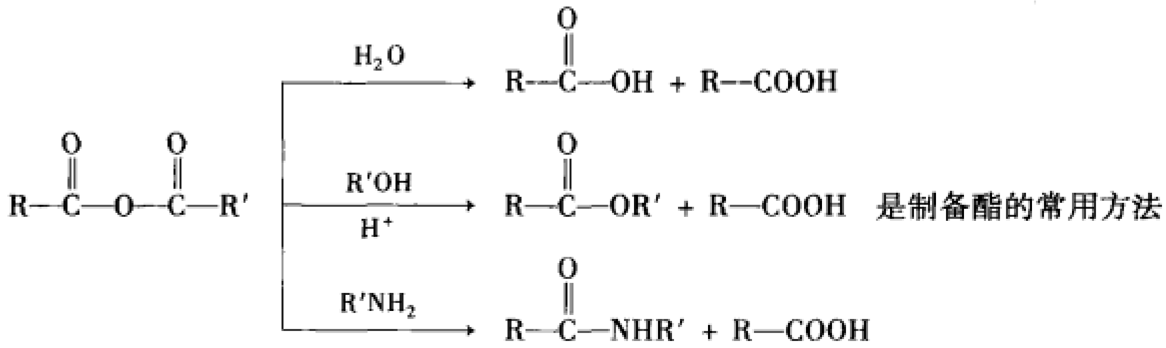


☆ 强的亲核试剂、好的离去基团、羧基碳上高的电正性及小的空间阻碍有利于反应的进行。

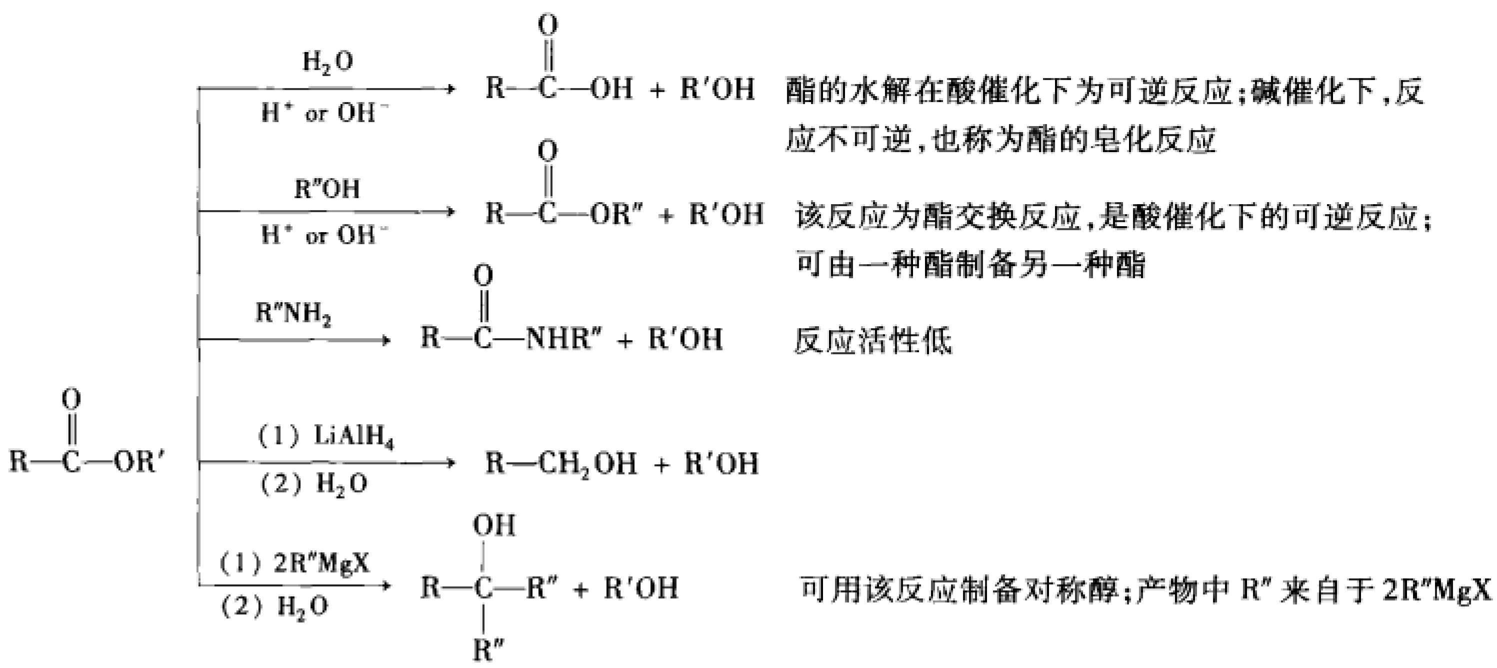
（1）酰氯的反应：



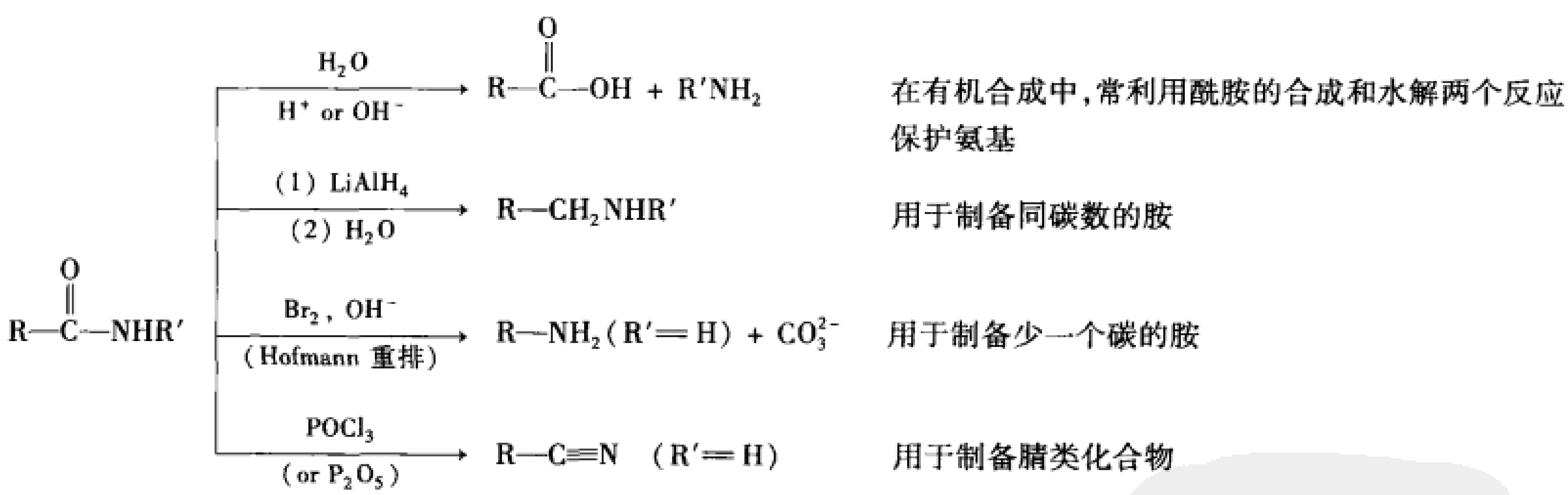
（2）酸酐的反应：



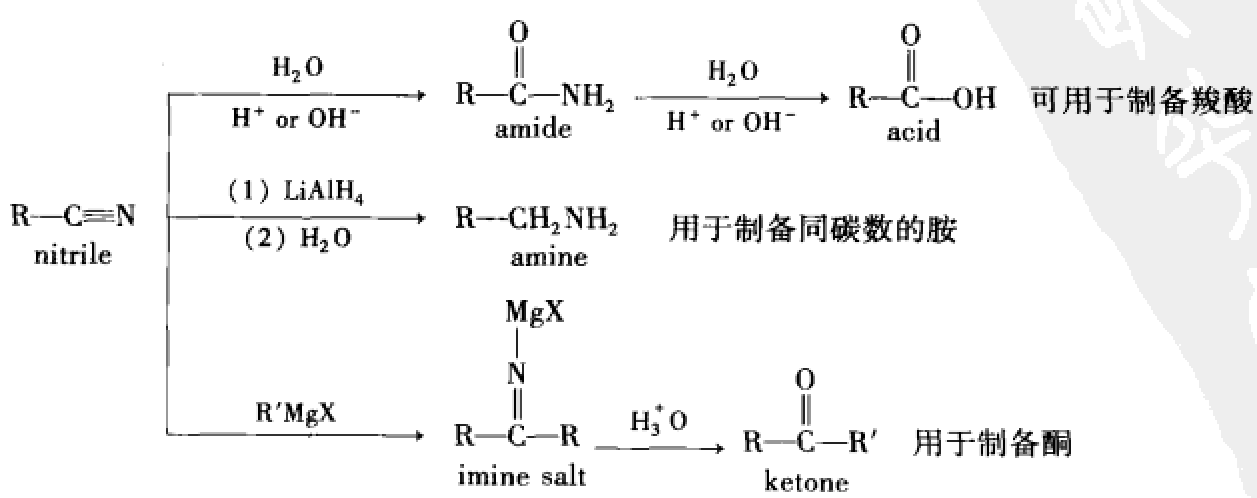
（3）酯的反应：



（4）酰胺的反应：



（5）腈的反应：



☆ 腈可认为是羧酸的衍生物，因为腈中的碳和羧酸中的碳有相同的氧化态，并且腈很容易转化为其他的羧酸衍生物。

Essential Problem-Solving Skills in Chapter 22

1. Compare the physical properties of acid derivatives, and explain the unusually high boiling points and melting points of amides.
2. Interpret the spectra of acid derivatives, and use the spectral information to determine the structures. Show how the carbonyl stretching frequency in the IR depends on the structure of the acid derivative.
3. Show how acid derivatives are easily interconverted by nucleophilic acyl substitution from more reactive derivatives to less reactive derivatives. Show how acid chlorides serve as activated intermediates to convert acids to acid derivatives.
4. Show how acid catalysis is used to synthesize acid derivatives, as in the Fischer esterification and in transesterification. Propose mechanisms for these reactions.
5. Show how acid derivatives hydrolyze to carboxylic acids, and explain why either acid or base is a suitable catalyst for the hydrolysis. Propose mechanisms for these hydrolyses.
6. Show what reagents are used to reduce acid derivatives, and show the products of reduction.
7. Show what products result from the addition of Grignard and organolithium reagents to acid derivatives, and propose mechanisms for these reactions.
8. Summarize the importance, uses, and special reactions of each type of acid derivative.

Study Problems

22–14 Predict the major products formed when benzoyl chloride (PhCOCl) reacts with the following reagents.

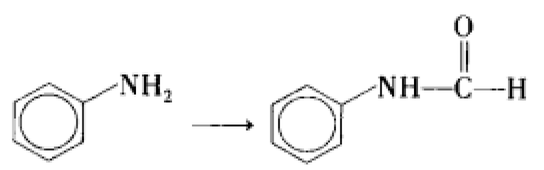
(a) ethanol (b) sodium acetate (c) aniline
(d) anisole and aluminum chloride
(e) excess phenylmagnesium bromide, then dilute acid (f) $LiAl(O\text{-}t\text{-}Bu)_3H$

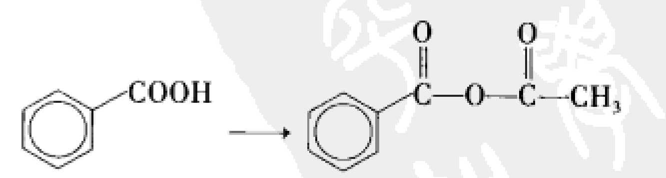
22–15 Acid-catalyzed transesterification and Fischer esterification take place by nearly identical mechanisms. Transesterification can also take place by a base-catalyzed mechanism, but all attempts at base-catalyzed Fischer esterification (using $^-OR''$, for example) seem doomed to failure. Explain why Fischer esterification cannot be catalyzed by base.

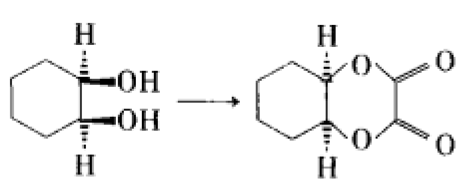
22–16 Predict the products of the following reactions.

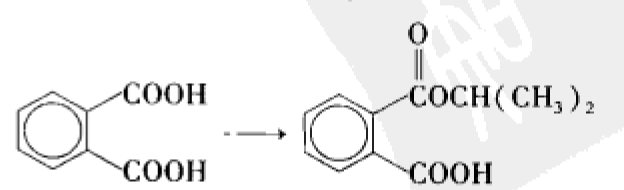
(a) phenol + acetic anhydride (b) phenol + acetic formic anhydride
(c) aniline + phthalic anhydride (d) anisole + succinic anhydride and aluminum chloride
(e) $Ph-CH(OH)-CH_2-NH_2$ + 1 equivalent of acetic anhydride
(f) $Ph-CH(OH)-CH_2-NH_2$ + excess acetic anhydride

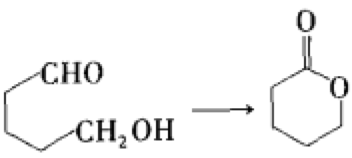
22–17 Show how you would accomplish the following syntheses in good yields.

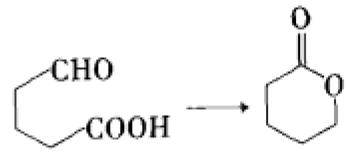
(a) 

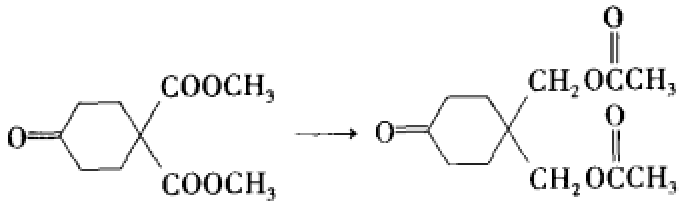
(b) 

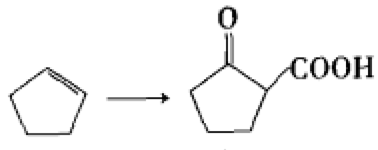
(c) 

(d) 

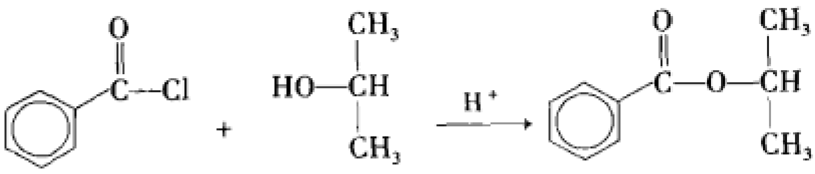
(e) 

(f) 

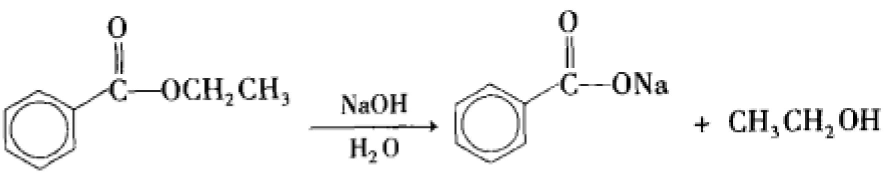
(g) 

(h) 

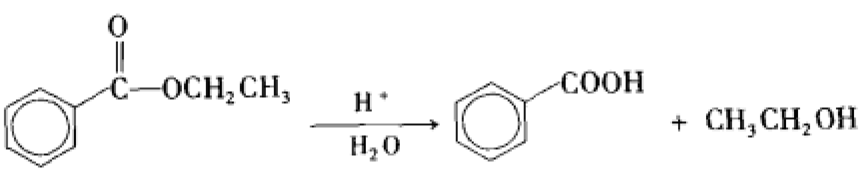
22–18 Propose mechanisms for the following reactions.

(a) 

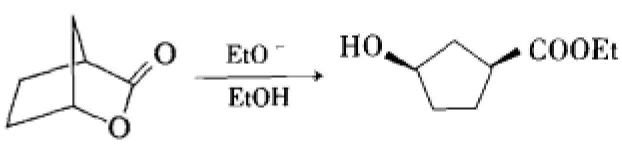
benzoyl chloride isopropyl alcohol isopropyl benzoate

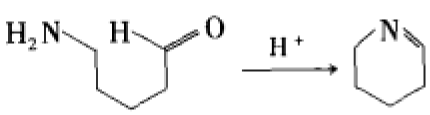
(b) 

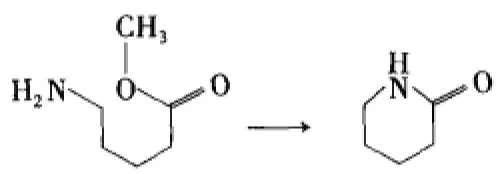
ethyl benzoate sodium benzoate ethanol

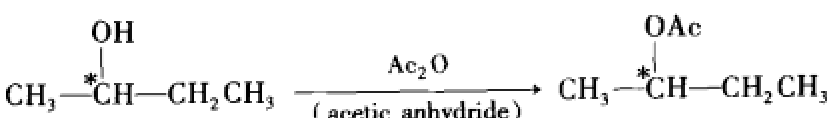
(c) 

ethyl benzoate benzoic acid ethanol

(d) 

(e) 

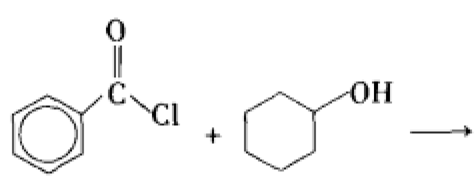
(f) 

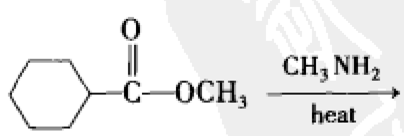
(g) 

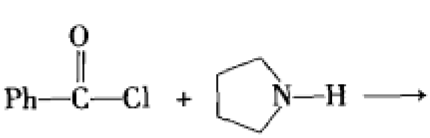
(R)-2-butanol 2-butyl acetate

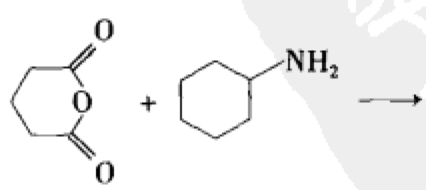
Does this reaction proceed with retention, inversion, or racemization of the asymmetric carbon atom?

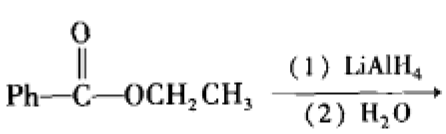
22–19 Predict the products of the following reactions.

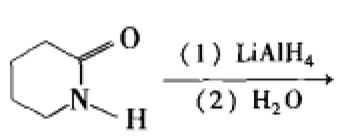
(a) 

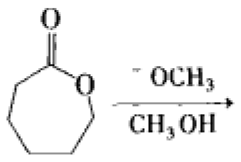
(b) 

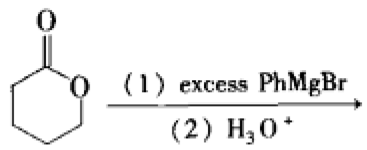
(c) 

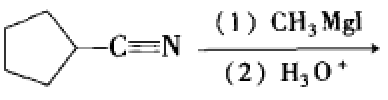
(d) 

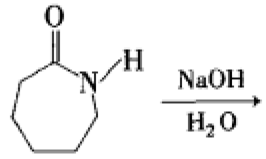
(e) 

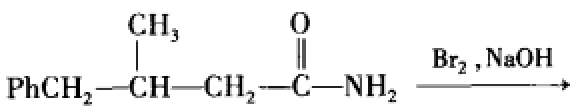
(f) 

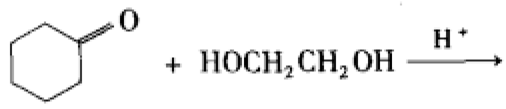
(g) 

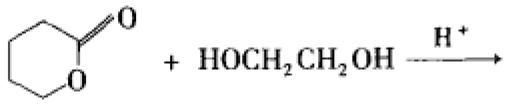
(h) 

(i) 

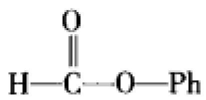
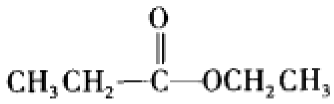
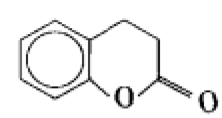
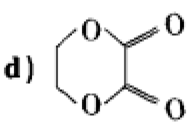
(j) 

(k) 

(l) 

(m) 

22−20 Predict the products of saponification of the following esters.

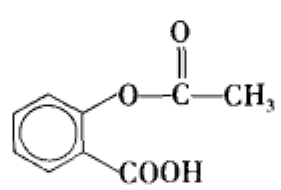
(a)  (b)  (c)  (d) 

22−21 An ether extraction of nutmeg gives large quantities of *trimyristin*, a waxy crystalline solid of melting point 57 ℃. The IR spectrum of trimyristin shows a very strong absorption at 1 733 cm^{-1}. Basic hydrolysis of trimyristin gives 1 equivalent of glycerol and 3 equivalents of myristic acid (tetradecanoic acid).

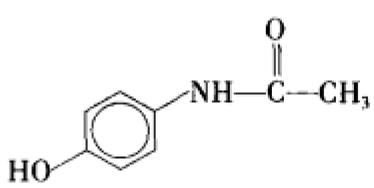
(a) Draw the structure of trimyristin.

(b) Predict the products formed when trimyristin is treated with lithium aluminum hydride, followed by aqueous hydrolysis of the aluminum salts.

22−22 Two widely used pain relievers are aspirin and acetaminophen. Show how you would synthesize these drugs from phenol.



aspirin



acetaminophen

22−23 Show how you would accomplish the following syntheses. Some of these conversions may require more than one step.

(a) isopentyl alcohol → isopentyl acetate (banana oil)

(b) 3-ethylpentanoic acid → 3-ethylpentanenitrile

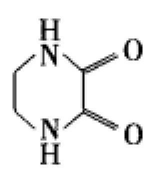
(c) isobutylamine → *N*-isobutylformamide

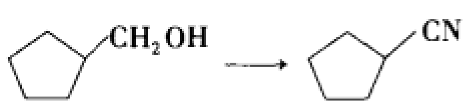
(d) ethyl acetate → 3-methyl-3-pentanol

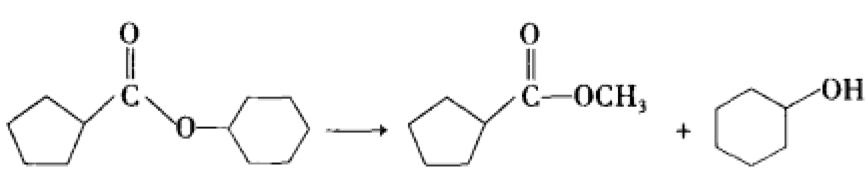
(e) pyrrolidine → *N*-methylpyrrolidine

(f) cyclohexylamine → *N*-cyclohexylacetamide

(g) bromocyclohexane → dicyclohexylmethanol

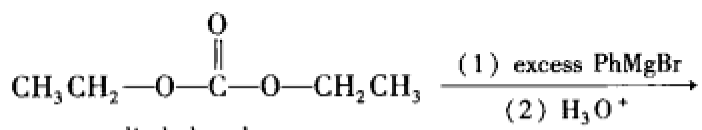
(h) dimethyl oxalate → 

(i) 

(j) 

22−24 Grignard reagents add to carbonate esters as they add to other esters.

(a) Predict the major product of the following reaction.



diethyl carbonate

(b) Show how you would synthesize 3−ethyl−3−pentanol using diethyl carbonate and ethyl bromide as your only organic reagents.

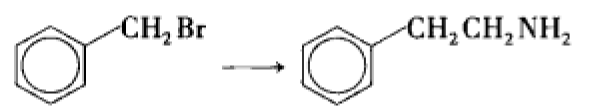
***22−25** One mole of acetyl chloride is added to a liter of triethylamine, resulting in a vigorous exothermic reaction. Once the reaction mixture has cooled, 1 mol of ethanol is added. Another vigorous exothermic reaction results. The mixture is analyzed and found to contain triethylamine, ethyl acetate, and triethylammonium chloride. Propose mechanisms for the two exothermic reactions.

22−26 Show how you would accomplish the following multistep syntheses, using the indicated starting material and any necessary reagents.

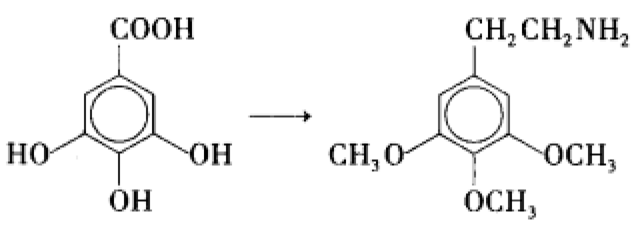
(a) 6-hepten-1-ol ⟶ ε-caprolactone

(b) methoxybenzene ⟶ *p*-methoxybenzamide

(c)

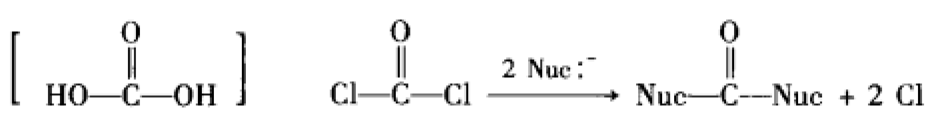


(d)



gallic acid mescaline

22−27 Phosgene is the acid chloride of carbonic acid. Although phosgene was used as a war gas in World War I, it is now used as a reagent for the synthesis of many useful products. Phosgene reacts like other acid chlorides, but it can react twice.



carbonic acid phosgene

Predict the products formed when phosgene reacts with

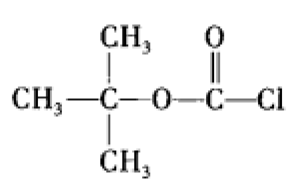
(a) excess ethanol

(b) excess methylamine

(c) 1 equivalent of methanol, followed by 1 equivalent of aniline

(d) ethylene glycol

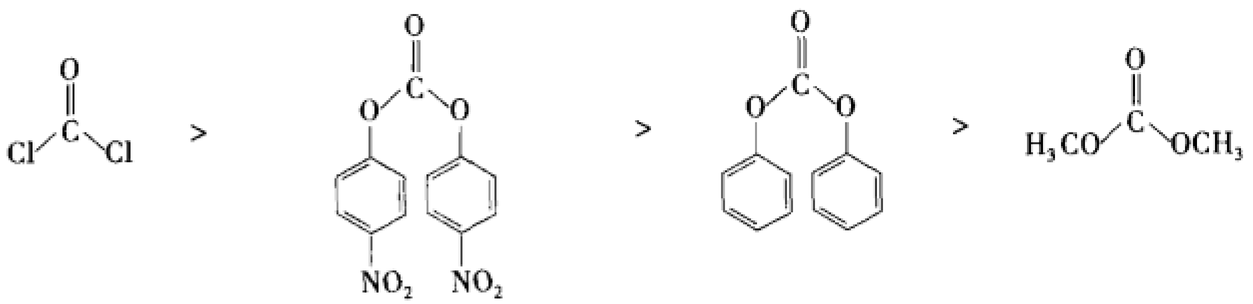
(e) *t*-Butyloxycarbonyl chloride is an important reagent for the synthesis of peptides and proteins (Chapter 25). Show how you would use phosgene to synthesize *t*-butyloxycarbonyl chloride.



t-butyloxycarbonyl chloride

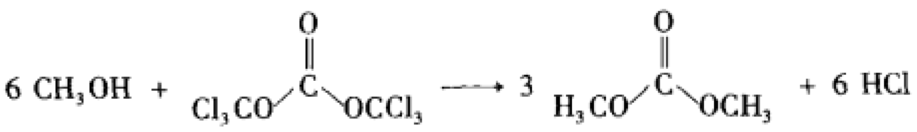
22−28 Phosgene (a toxic and corrosive gas) is inconvenient and sometimes hazardous to use as a reagent. Several phosgene substitutes have been developed.

(a) The following phosgene substitutes are shown in order of decreasing reactivity toward nucleophilic attack. Explain this order of reactivity.



phosgene *fastest* > *bis* (*p*-nitrophenyl) carbonate > diphenyl carbonate > dimethyl carbonate *slowest*

(b) Another phosgene substitute is triphosgene, a stable solid that can be handled more easily than phosgene. Write a mechanism to show how triphosgene reacts with methanol to form 3 equivalents of dimethyl carbonate.



triphosgene dimethyl carbonate

22−29 In Section 22−9, we saw that Sevin® insecticide is made by the reaction of 1-naphthol with methyl isocyanate. A Union Carbide plant in Bhopal, India, once used this process to make Sevin® for use as an agricultural insecticide. On December 3, 1984, either by accident or by sabotage, a valve was opened that admitted water to a large tank of methyl isocyanate. The pressure and temperature within the tank rose dramatically, and pressure-relief valves opened to keep the tank from bursting. A large quantity of methyl isocyanate rushed out through the pressure-relief valves, and the vapors flowed with the breeze into populated areas, killing about 2 500 people and injuring many more.

(a) Write an equation for the reaction that took place in the tank. Explain why the pressure and temperature rose dramatically.

(b) Propose a mechanism for the reaction you wrote in part (a).

(c) Propose an alternative synthesis of Sevin®. Unfortunately, the best alternative synthesis uses phosgene, a gas that is even more toxic than methyl isocyanate.

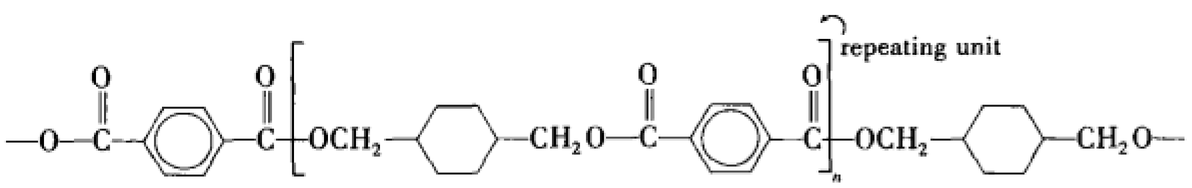
22−30 The structures of six useful polymers are shown, together with some of their best-known products. In each case,

1. Determine the kind of polymer (polyamide, polyester, etc.).

2. Draw the structures of the monomers that would be released by complete hydrolysis.

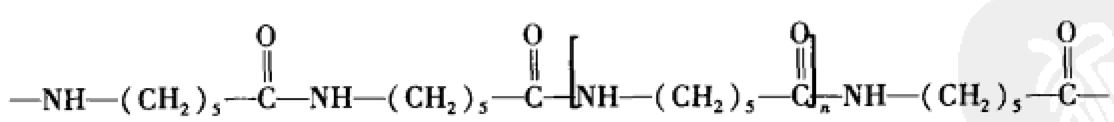
3. Suggest what monomers or stable derivatives of the monomers might be used to make these polymers.

(a)



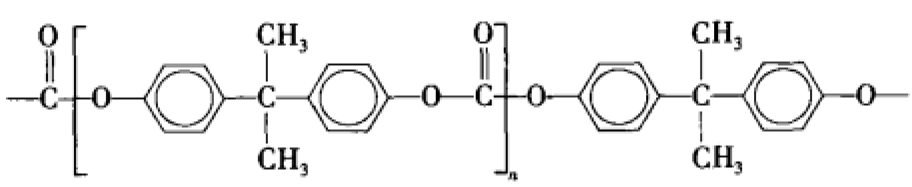
soft, sheer fabrics; synthetic silk

(b)



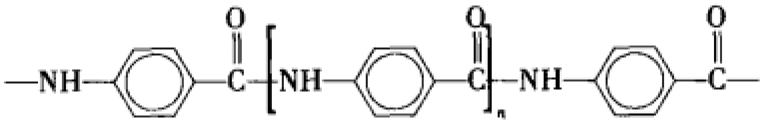
climbing ropes, violin strings

(c)

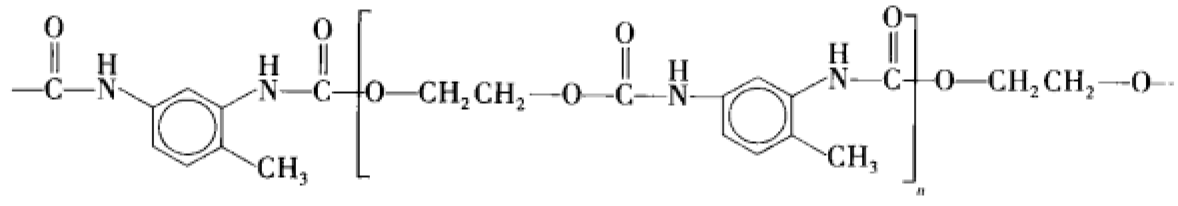


crash helmets, bulletproof "glass"

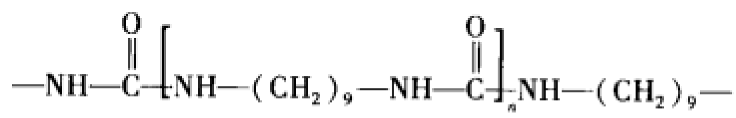
(d)



high-strength fabrics; bulletproof vests

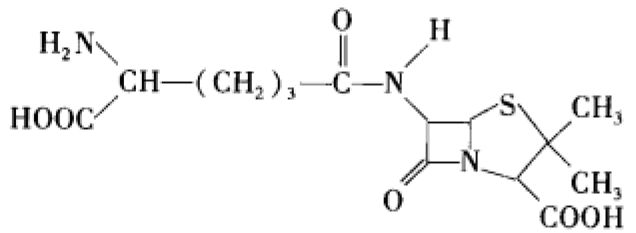
(e) 

skateboard wheels, foam mattresses

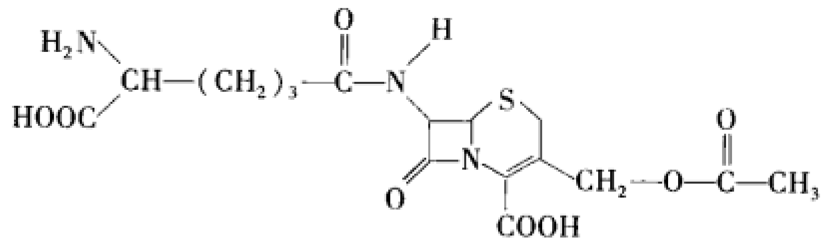
(f) 

fishing lines and nets

22–31 The following two compounds, which exhibit powerful antibacterial activity, were isolated from the fungus *Cephalosporium acremonium* in 1948 from the sea near a sewage outlet on the Sardinian coast.



cephalosporin N



cephalosporin C

(a) Name the class of antibiotics represented by each compound.

(b) After its structure had been determined, one of these compounds came to be known by a more appropriate name. Determine which compound is poorly named, and replace the inappropriate part of the name.

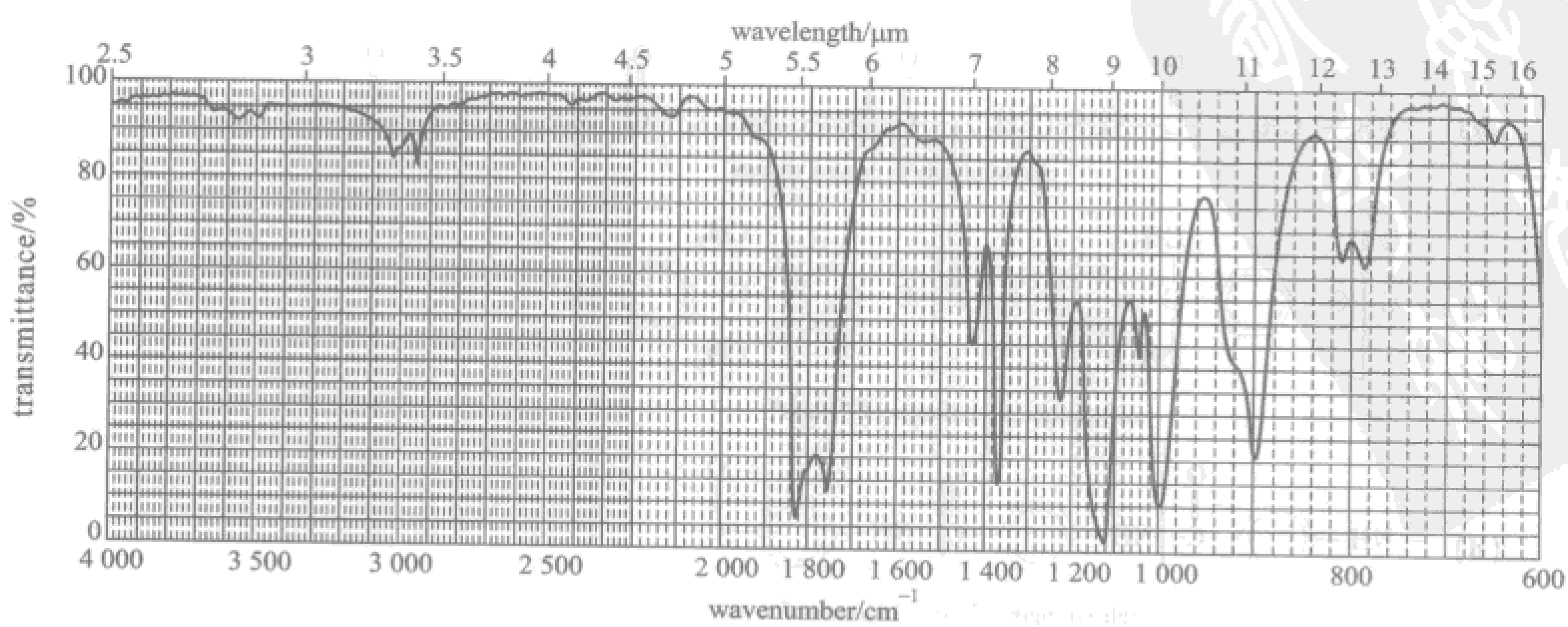
***22–32** Methyl *p*-nitrobenzoate has been found to undergo saponification faster than methyl benzoate.

(a) Consider the mechanism of saponification, and explain the reasons for this rate enhancement.

(b) Would you expect methyl *p*-methoxybenzoate to undergo saponification faster or slower than methyl benzoate?

22–33 A student has just added ammonia to hexanoic acid and has begun to heat the mixture when he is called away to the telephone. After a long telephone conversation, he returns to find that the mixture has overheated and turned black. He distills the volatile components and recrystallizes the solid residue. Among the components he isolates are compounds A (a liquid; molecular formula $C_6H_{11}N$) and B (a solid; molecular formula $C_6H_{13}NO$). The infrared spectrum of A shows a strong, sharp absorption at 2247 cm^{-1}. The infrared spectrum of B shows absorptions at 3390 cm^{-1}, 3200 cm^{-1}, and 1665 cm^{-1}. Determine the structures of compounds A and B.

22–34 A chemist was called to an abandoned aspirin factory to determine the contents of a badly corroded vat. Knowing that two salvage workers had become ill from breathing the fumes, she put on her breathing apparatus as soon as she noticed an overpowering odor like that of vinegar but much more pungent. She entered the building and took a sample of the contents of the vat. The mass spectrum showed a molecular weight of 102, and the NMR spectrum showed only a singlet at $\delta 2.15$. The IR spectrum, which appears here, left no doubt about the identity of the compound. Identify the compound, and suggest a method for its safe disposal.



Chapter 23

Condensations and Alpha Substitutions of Carbonyl Compounds

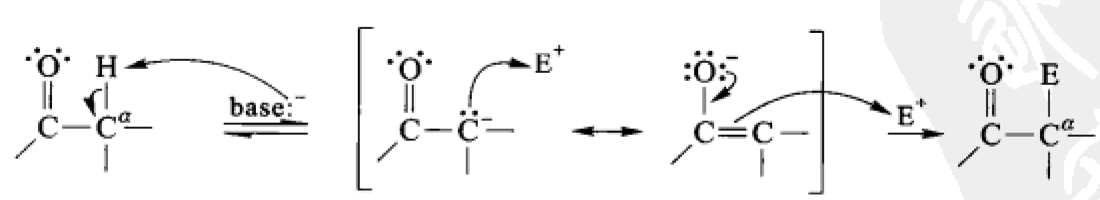
23-1 Introduction

Up to now, we have studied two of the main types of carbonyl reactions: nucleophilic addition and nucleophilic acyl substitution. In these reactions, the carbonyl group serves as an *electrophile* by accepting electrons from an attacking nucleophile. In this chapter, we consider two more types of reactions: substitution at the carbon atom next to the carbonyl group (called alpha substitution) and carbonyl condensations.

Alpha (α) substitutions involve the replacement of a hydrogen atom at the **α carbon atom** (the carbon next to the carbonyl group) by some other group. The α hydrogen is more acidic because the enolate ion that results from its removal is resonance-stabilized, with the negative charge delocalized over the α carbon atom and the carbonyl oxygen atom. Alpha substitutions generally take place when the carbonyl compound is converted to its enolate ion or its enol tautomer. Both of these species have lost a hydrogen atom at the alpha position, and both are *nucleophilic*. Nucleophilic attack on an electrophile forms a product in which the electrophile has replaced one of the hydrogens on the α carbon atom.

MECHANISM 23-1 Alpha Substitution

Step 1: Deprotonation of α carbon to form an enolate. ***Step 2***: Nucleophilic attack on an electrophile.

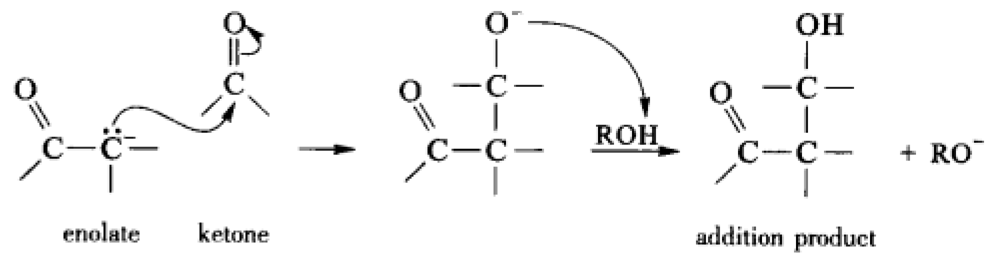


enolate ion（烯醇化离子）

Carbonyl **condensations** are alpha substitutions where the electrophile is another carbonyl compound. If the electrophile is a ketone or an aldehyde, then the enolate ion adds to that carbonyl group in a nucleophilic addition. First, the enolate ion attacks the carbonyl group to form an alkoxide. Protonation of the alkoxide gives the addition product.

MECHANISM 23-2 Addition of an Enolate to Ketones and Aldehydes (a Condensation)

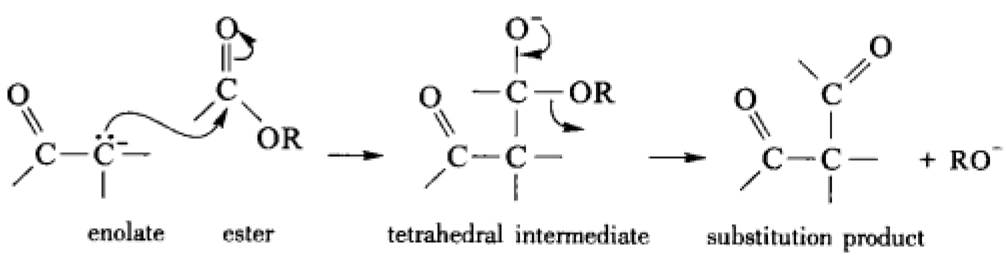
***Step 1*:** The enolate adds to the carbonyl group. ***Step 2*:** Protonation of the alkoxide.



If the electrophile is an ester, then the ester undergoes a nucleophilic acyl substitution with the enolate ion serving as the nucleophile. First, the enolate adds to the ester to form a tetrahedral intermediate. Elimination of the leaving group (alkoxide) gives the substitution product.

MECHANISM 23-3 Substitution of an Enolate on an Ester (a Condensation)

***Step 1*:** Addition of the enolate. ***Step 2*:** Elimination of the alkoxide.



Alpha substitutions and condensations of carbonyl compounds are some of the most common methods for forming carbon-carbon bonds. A wide variety of compounds can participate as nucleophiles or electrophiles (or both) in these reactions, and many useful products can be made. We begin our study of these reactions by considering the structure and formation of enols and enolate ions.

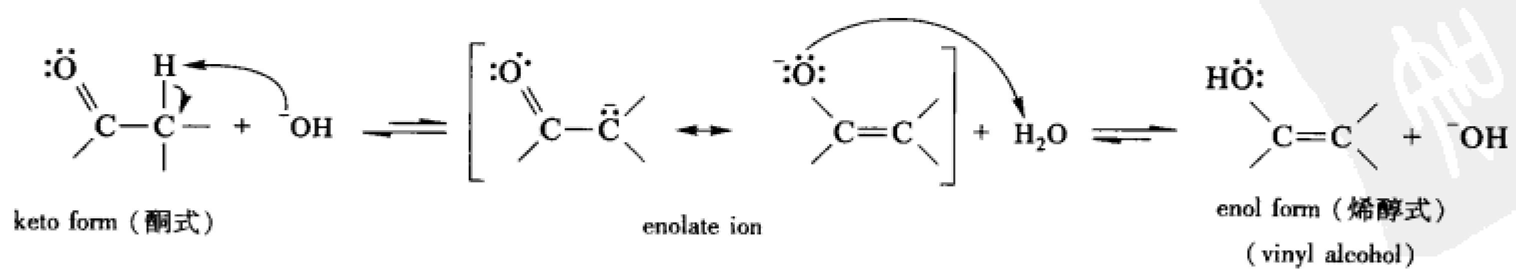
23-2 Enols and Enolate Ions

23-2A Keto-Enol Tautomerism

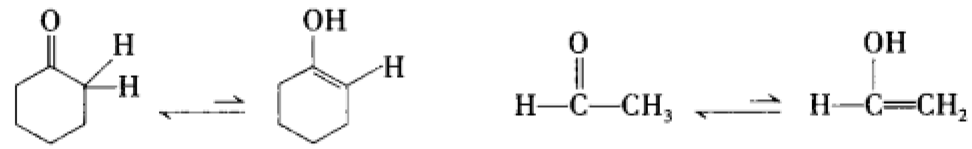
In the presence of strong bases, ketones and aldehydes act as weak proton acids. A proton on the α carbon is abstracted to form a resonance-stabilized **enolate ion** with the negative charge spread over a carbon atom and an oxygen atom. Reprotonation can occur either on the α carbon (returning to the **keto** form) or on the oxygen atom, giving a vinyl alcohol, the **enol** form.

MECHANISM 23-4 Base-Catalyzed Keto-Enol Tautomerism

***Step 1*:** Deprotonation of α C. ***Step 2*:** Reprotonation on O.



In this way, base catalyzes an equilibrium between isomeric keto and enol forms of a carbonyl compound. For simple ketones and aldehydes, the keto form predominates. Therefore, a vinyl alcohol (an enol) is best described as an alternative isomeric form of a ketone or aldehyde. We saw that an enol intermediate, formed by hydrolysis of an alkyne, quickly isomerizes to its keto form.



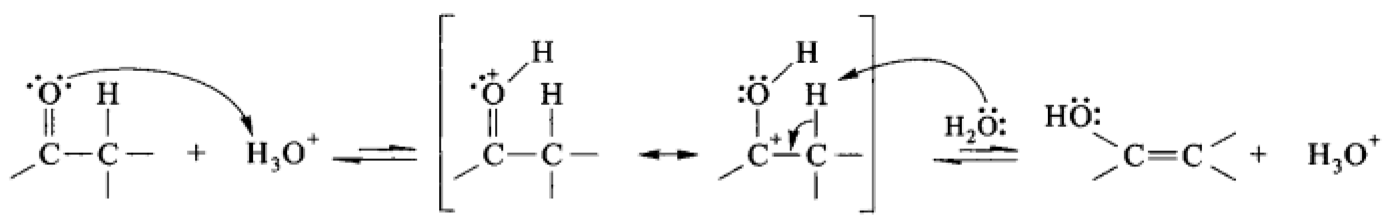
keto form (99.99%) | enol form (0.01%) | keto form (99.95%) | enol form (0.05%)

This type of isomerization, occurring by the migration of a proton and the movement of a double bond, is called **tautomerism**, and the isomers that interconvert are called **tautomers**. Don't confuse tautomers with resonance forms. Tautomers are true isomers (different compounds) with their atoms arranged differently. Under the right circumstances, with no catalyst present, either individual tautomeric form may be isolated. Resonance forms are different representations of the *same* structure, with all the atoms in the same places, showing how the electrons are delocalized.

Keto-enol tautomerism is also catalyzed by acid. In acid, a proton is moved from the α carbon to oxygen by first protonating oxygen and then removing a proton from carbon.

MECHANISM 23-5 Acid-Catalyzed Keto-Enol Tautomerism

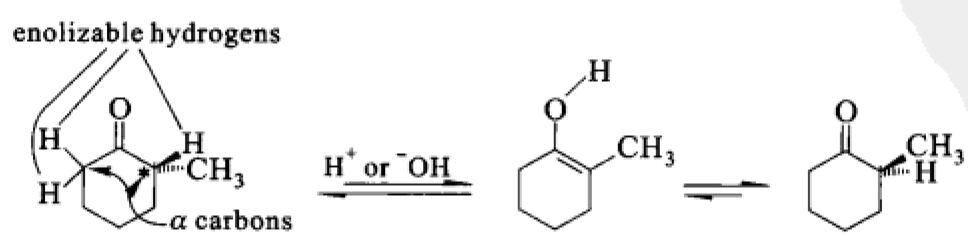
Step 1: An acid protonates the carbonyl oxygen. ***Step 2***: Deprotonation on C gives the enol form.



keto form | protonated carbonyl | enol form

Compare the base-catalyzed and acid-catalyzed mechanisms shown for keto-enol tautomerism. In base, the proton is removed from carbon, then replaced on oxygen. In acid, oxygen is protonated first, then carbon is deprotonated. Most proton-transfer mechanisms work this way. In base, the proton is removed from the old location, then replaced at the new location. In acid, protonation occurs at the new location, followed by deprotonation at the old location.

In addition to its mechanistic importance, keto-enol tautomerism affects the stereochemistry of ketones and aldehydes. A hydrogen atom on an α carbon may be lost and regained through keto-enol tautomerism; such a hydrogen is said to be **enolizable**. If an asymmetric carbon atom has an enolizable hydrogen atom, a trace of acid or base allows that carbon to invert its configuration, with the enol serving as the intermediate. A racemic mixture (or an equilibrium mixture of diastereomers) is the result.



(*R*) configuration [(*R*) 构型] | enol (achiral) [烯醇(非手性)] | (*S*) configuration [(*S*)构型]

PROBLEM 23-1

Phenylacetone can form two different enols.

(a) Show the structures of these enols.

(b) Predict which enol will be present in the larger concentration at equilibrium.

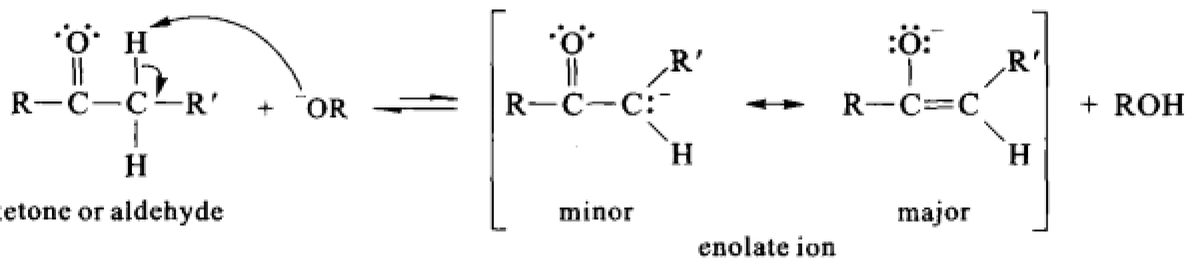
(c) Propose mechanisms for the formation of the two enols in acid and in base.

PROBLEM 23-2

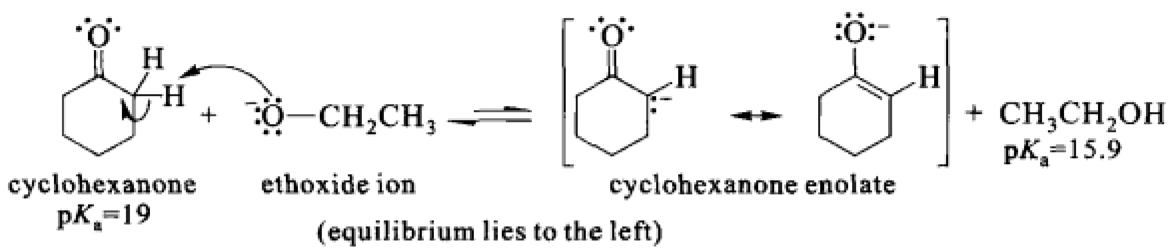
Show each step in the mechanism of the acid-catalyzed interconversion of (*R*)-and (*S*)-2-methylcyclohexanone.

23-2B Formation and Stability of Enolate Ions

A carbonyl group dramatically increases the acidity of the protons on the α carbon atom because most of the enolate ion's negative charge resides on the electronegative oxygen atom. The pK_a for removal of an α proton from a typical ketone or aldehyde is about 20, showing that a typical ketone or aldehyde is much more acidic than an alkane or an alkene ($pK_a > 40$), or even an alkyne ($pK_a = 25$). Still, a ketone or aldehyde is less acidic than water ($pK_a = 15.7$) or an alcohol ($pK_a = 16$ to 18). When a simple ketone or aldehyde is treated with hydroxide ion or an alkoxide ion, the equilibrium mixture contains only a small fraction of the deprotonated, enolate form.



Example



Even though the equilibrium concentration of the enolate ion may be small, it serves as a useful, reactive nucleophile. When an enolate reacts with an electrophile (other than a proton), the enolate concentration decreases, and the equilibrium shifts to the right (Figure 23-1). Eventually, all the carbonyl compound reacts

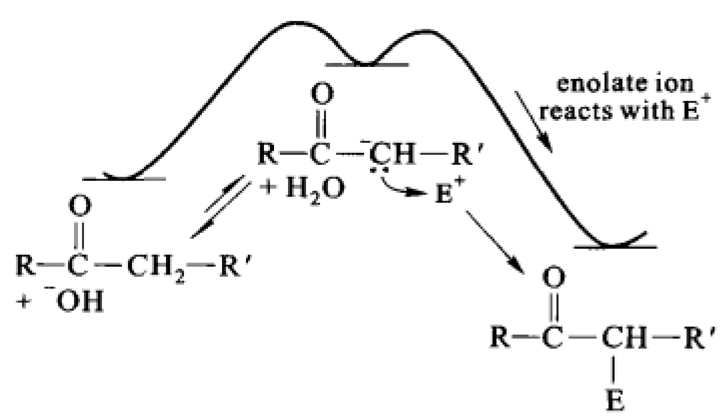


Figure 23-1 Reaction of the enolate ion with an electrophile removes it from the equilibrium, shifting the equilibrium to the right.

via a low concentration of the enolate ion.

PROBLEM 23-3

Give the important resonance forms for the enolate ion of

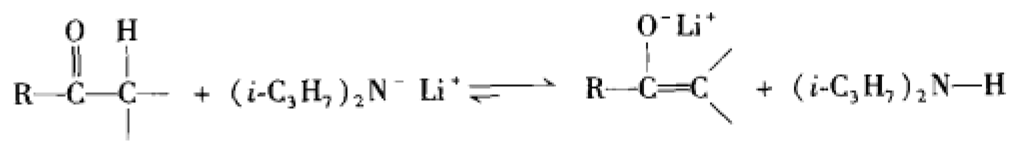
(a) acetone (b) cyclopentanone (c) 2,4-pentanedione

Sometimes this equilibrium mixture of enolate and base won't work, usually because the base (hydroxide or alkoxide) reacts with the electrophile faster than the enolate does. In these cases, we need a base that reacts completely to convert the carbonyl compound to its enolate before adding the electrophile. Although sodium hydroxide and alkoxides are not sufficiently basic, powerful bases are available to convert a carbonyl compound completely to its enolate. The most effective and useful base for this purpose is lithium diisopropylamide (LDA), the lithium salt of diisopropylamine. LDA is made by using an alkyllithium reagent to deprotonate diisopropylamine.

$$[(CH_3)_2CH]_2NH + C_4H_9Li \longrightarrow C_4H_{10} + [(CH_3)_2CH]_2N^- \ Li^+$$

diisopropylamine (二异丙基胺) + *n*-butyllithium (正丁基锂) ⟶ butane + lithium diisopropylamide (LDA) [二异丙基胺锂(LDA)]

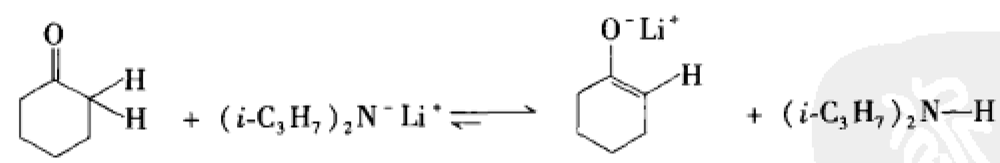
Diisopropylamine has a pK_a of about 36, showing that it is much *less* acidic than a typical ketone or aldehyde. By virtue of its two isopropyl groups, LDA is a bulky reagent. It does not easily attack a carbon atom or add to a carbonyl group. Thus, it is a powerful base, but not a strong nucleophile. When LDA reacts with a ketone, it abstracts the α proton to form the lithium salt of the enolate. We will see that these lithium enolate salts are very useful in synthesis.



ketone (p$K_a \approx 20$) + LDA ⇌ lithium salt of enolate + diisopropylamine (p$K_a = 36$)

(equilibrium lies to the right)

Example

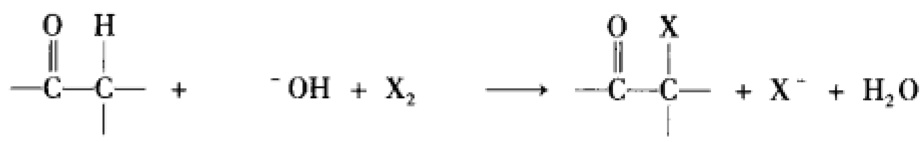


cyclohexanone (p$K_a = 19$) + LDA ⇌ lithium enolate of cyclohexanone (100%) + (p$K_a = 36$)

23-3 Alpha Halogenation of Ketones

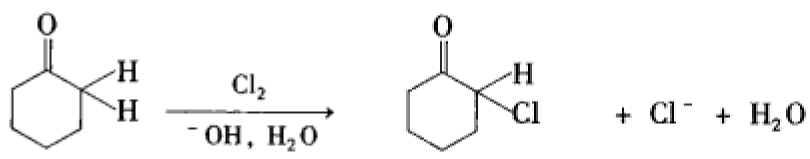
23-3A Base-Promoted α Halogenation

When a ketone is treated with a halogen and base, an α-halogenation reaction occurs.



ketone ($X_2 = Cl_2$, Br_2 , or I_2) α-haloketone

Example

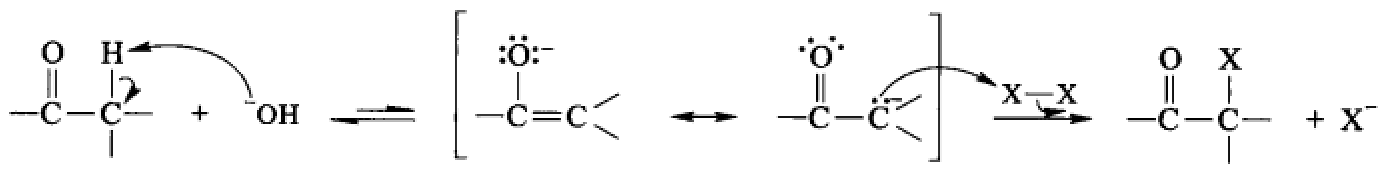


cyclohexanone 2-chlorocyclohexanone

The base-promoted halogenation takes place by a nucleophilic attack of an enolate ion on the electrophilic halogen molecule. The products are the halogenated ketone and a halide ion.

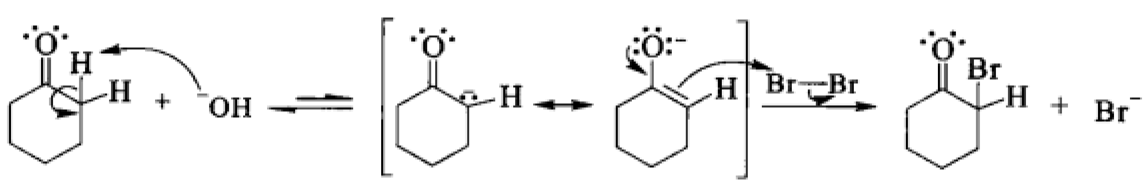
MECHANISM 23-6 Base-Promoted Halogenation

Step 1: Deprotonation of the α carbon forms the enolate ion. ***Step 2***: The enolate ion attacks the electrophilic halogen.



enolate ion + H_2O

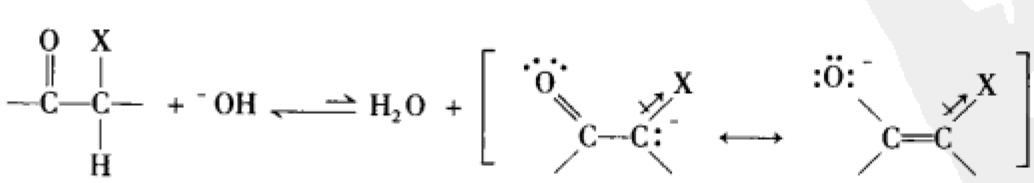
EXAMPLE: Base-promoted bromination of cyclohexanone.



enolate ion

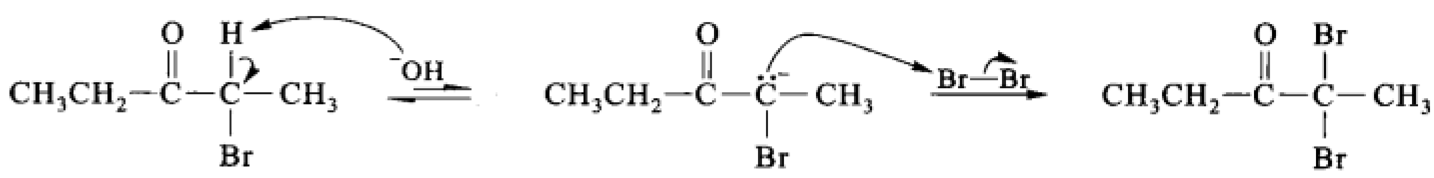
This reaction is called *base-promoted*, rather than base-catalyzed, because a full equivalent of the base is consumed in the reaction.

Multiple Halogenation In many cases, base-promoted halogenation does not stop with replacement of just one hydrogen. The product (the α-haloketone) is more reactive toward further halogenation than is the starting material, because the electronwithdrawing halogen stabilizes the enolate ion, enhancing its formation.



(enolate stabilized by X)

For example, bromination of 3-pentanone gives mostly 2,2-dibromo-3-pentanone. After one hydrogen is replaced by bromine, the enolate ion is stabilized by both the carbonyl group and the bromine atom. A second bromination takes place faster than the first. Notice that the second substitution takes place at the same carbon atom as the first, because that carbon atom bears the enolate-stabilizing halogen.



monobrominated ketone　　stabilized by Br　　second bromination

Because of this tendency for multiple halogenation, base-promoted halogenation is rarely used for the preparation of monohalo ketones. The acid-catalyzed procedure (discussed in Section 23-3C) is preferred.

PROBLEM 23-4

Propose a mechanism to show how acetophenone undergoes base-promoted chlorination to give trichloroacetophenone.

23-3B The Haloform Reaction

With most ketones, base-promoted halogenation continues until the α-carbon atom is completely halogenated. Methyl ketones have three α protons on the methyl carbon, and they undergo halogenation three times to give trihalomethyl ketones.

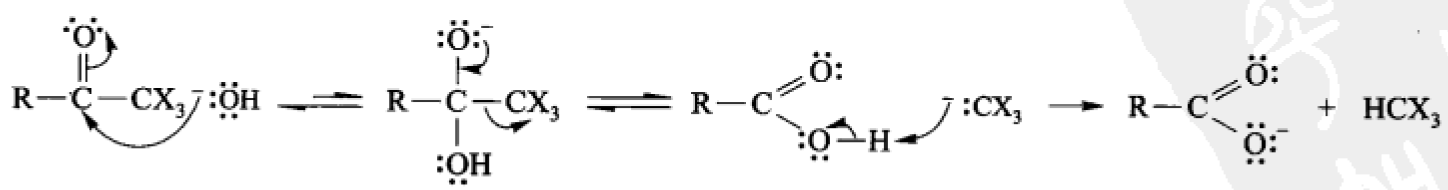
$$\underset{\text{methyl ketone}}{R-\overset{\overset{\large O}{\|}}{C}-CH_3} + 3X_2 + 3\,^{-}OH \longrightarrow \longrightarrow \longrightarrow \underset{\text{trihalomethyl ketone}}{R-\overset{\overset{\large O}{\|}}{C}-CX_3} + 3X^- + 3H_2O$$

With three electron-withdrawing halogen atoms, the trihalomethyl group can serve as a reluctant leaving group for nucleophilic acyl substitution. The trihalomethyl ketone reacts with hydroxide ion to give a tetrahedral intermediate that expels the trihalomethyl anion ($^-CX_3$), leaving a carboxylic acid. A fast proton exchange gives a carboxylate ion and a haloform (chloroform, $CHCl_3$; bromoform, $CHBr_3$; or iodoform, CHI_3). The overall reaction is called the **haloform reaction.**

MECHANISM 23-7　Final Steps of the Haloform Reaction

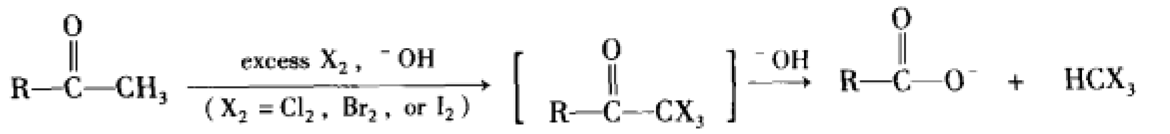
The conclusion of the haloform reaction is a nucleophilic acyl substitution, with hydroxide as the nucleophile and $^-CX_3$ as the leaving group.

***Step 1*:** Hydroxide adds to the carbonyl group.　***Step 2*:** $^-CX_3$ leaves.　***Step 3*:** Fast proton transfer from the acid.



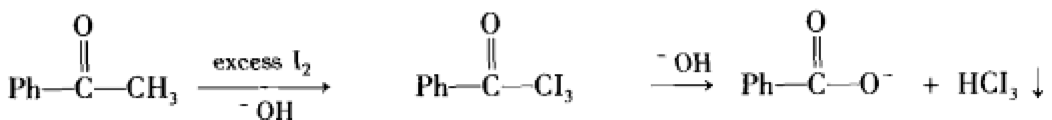
nucleophilic acyl substitution　　a carboxylate ion　　a haloform (卤仿)

The overall haloform reaction is summarized next. A methyl ketone reacts with a halogen under strongly basic conditions to give a carboxylate ion and a haloform.



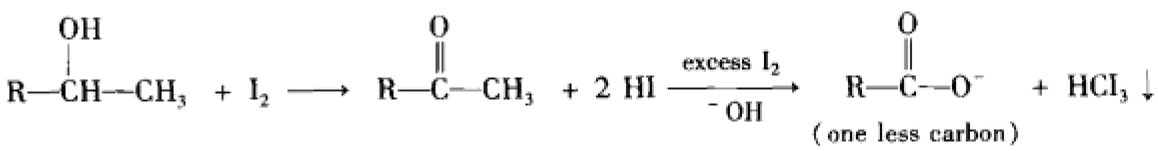
a methyl ketone — a trihalomethyl ketone (not isolated) — a carboxylate — a haloform (卤仿)

When the halogen is iodine, the haloform product (iodoform) is a solid that separates out as a yellow precipitate. This **iodoform test** identifies methyl ketones, which halogenate three times, then lose $^-CI_3$ to give iodoform.



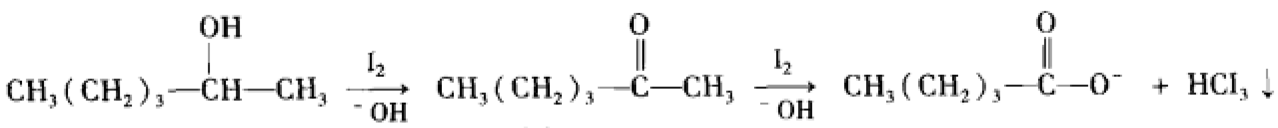
acetophenone (苯乙酮) — α,α,α-triiodoacetophenone (α, α, α-三碘代苯乙酮) — benzoate — iodoform (碘仿)

Iodine is an oxidizing agent, and an alcohol can give a positive iodoform test if it oxidizes to a methyl ketone. The iodoform reaction can convert such an alcohol to a carboxylic acid with one less carbon atom.



(one less carbon)

Example



2-hexanol — 2-hexanone — pentanoate

PROBLEM 23-5

Propose a mechanism for the reaction of methyl cyclohexyl ketone with excess bromine in the presence of sodium hydroxide.

PROBLEM 23-6

Predict the products of the following reactions.

(a) methyl cyclopentyl ketone + excess Cl_2 + excess NaOH

(b) 1-cyclopentylethanol + excess I_2 + excess NaOH

(c) propiophenone + excess Br_2 + excess NaOH

PROBLEM 23-7

Which compounds will give a positive iodoform test?

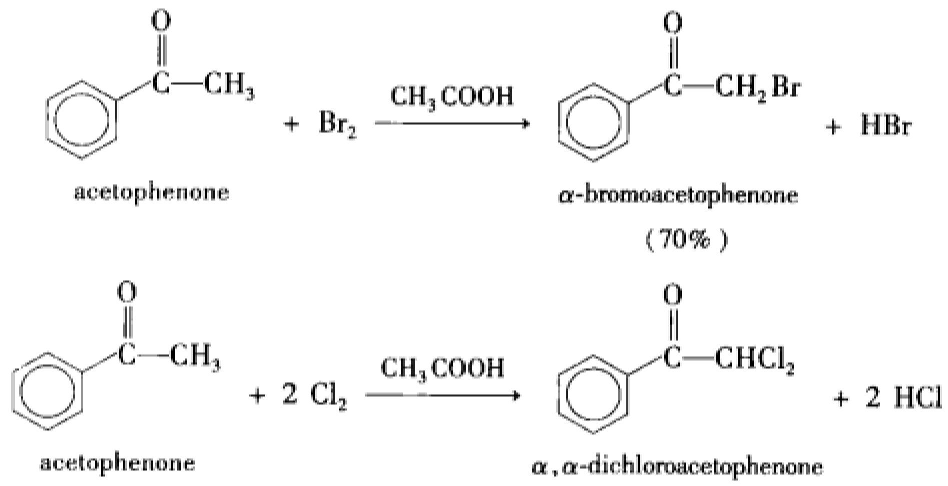
(a) 1-phenylethanol **(b)** 2-pentanone **(c)** 2-pentanol

(d) 3-pentanone **(e)** acetone **(f)** isopropyl alcohol

23-3C Acid-Catalyzed Alpha Halogenation

Ketones also undergo acid-catalyzed α halogenation. One of the most effective procedures is to dissolve the

ketone in acetic acid, which serves as both the solvent and the acid catalyst. In contrast with basic halogenation, acidic halogenation can selectively replace just one hydrogen or more than one, depending on the amount of the halogen added.

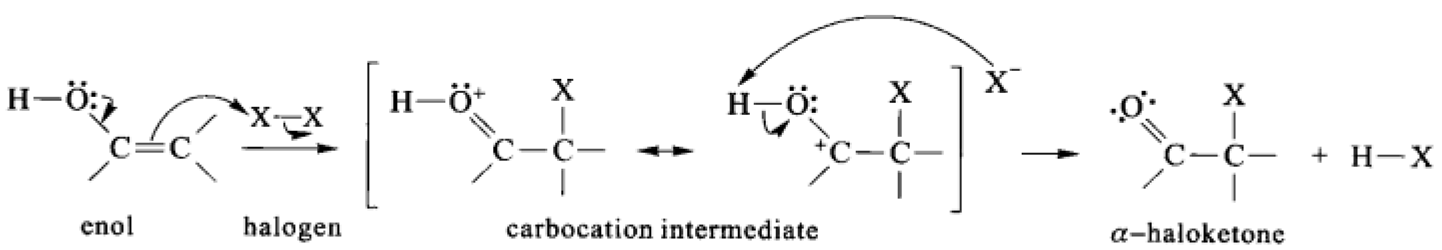


The mechanism of acid-catalyzed halogenation involves attack of the enol form on the electrophilic halogen molecule. Loss of a proton gives the α-haloketone and the hydrogen halide.

MECHANISM 23−8 Acid-Catalyzed Alpha Halogenation

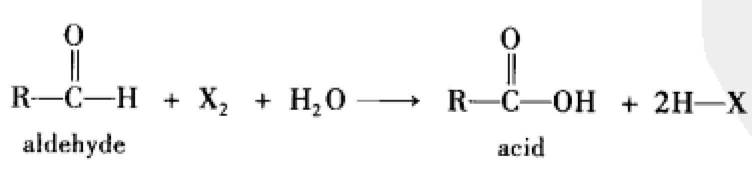
Acid-catalyzed halogenation results when the enol form of the carbonyl compound serves as a nucleophile to attack the halogen (a strong electrophile). Deprotonation gives the α-haloketone.

Step 1: The enol attacks the halogen. ***Step 2***: Deprotonation.



This reaction is similar to the attack of an alkene on a halogen, resulting in addition of the halogen across the double bond. The pi bond of an enol is more reactive toward halogens, however, because the carbocation that results is stabilized by resonance with the enol —OH group. Loss of the enol proton converts the intermediate to the product, an α-haloketone.

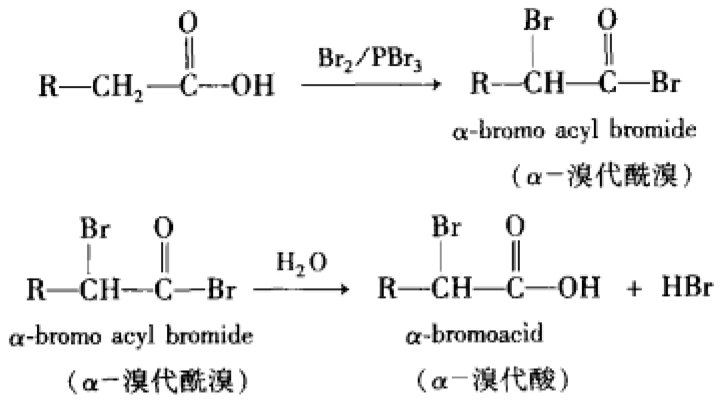
Unlike ketones, aldehydes are easily oxidized, and halogens are strong oxidizing agents. Attempted halogenation of aldehydes usually results in oxidation to carboxylic acids.



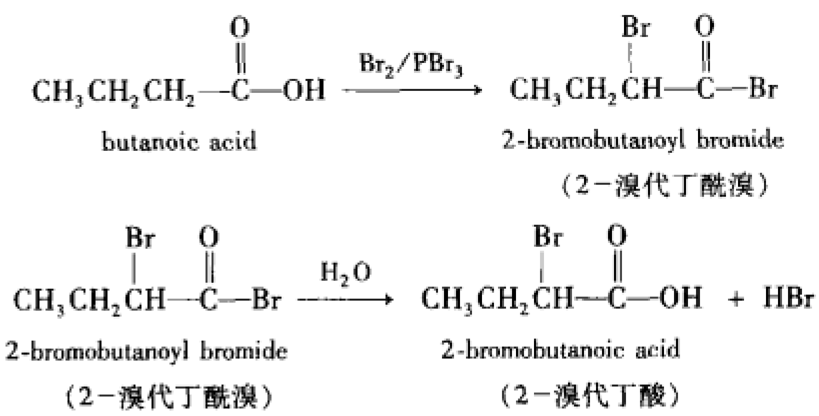
23−4 α Bromination of Acids: The HVZ Reaction

The **Hell-Volhard-Zelinsky (HVZ) reaction** replaces a hydrogen atom with a bromine atom on the α carbon of a carboxylic acid. The carboxylic acid is treated with bromine and phosphorous tribromide, followed by water to hydrolyze the intermediate α-bromo acyl bromide.

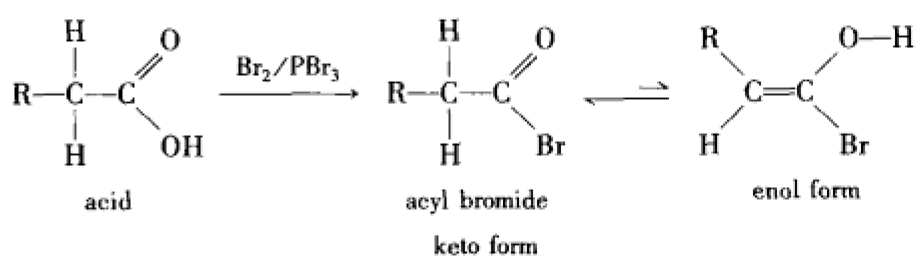
The HVZ reaction



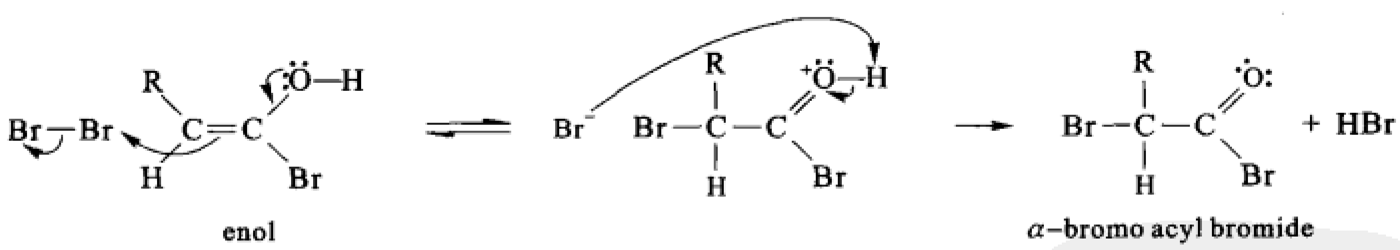
Example



The mechanism is similar to other acid-catalyzed α halogenations; the enol form of the acyl bromide serves as a nucleophilic intermediate. The first step is formation of acyl bromide, which enolizes more easily than does the acid.



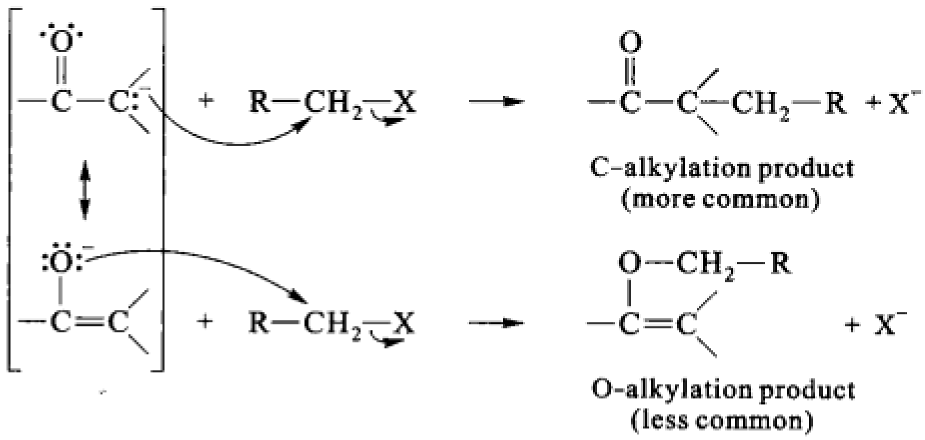
The enol is nucleophilic, attacking bromine to give the α-brominated acyl bromide.



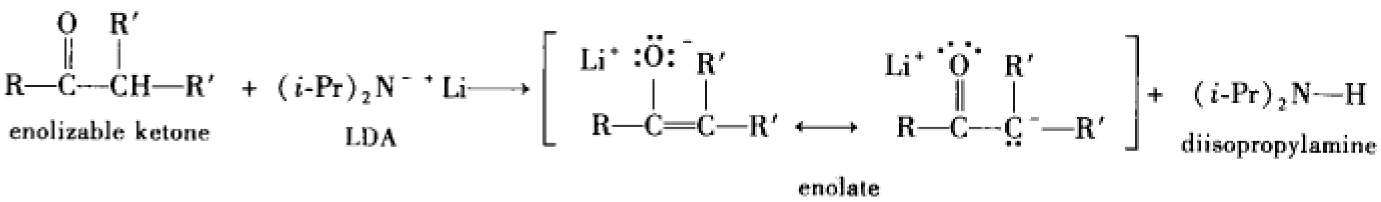
If a derivative of the α-bromoacid is desired, the α-bromo acyl bromide serves as an activated intermediate (similar to an acid chloride) for the synthesis of an ester, amide, or other derivative. If the α-bromoacid itself is needed, a water hydrolysis completes the synthesis.

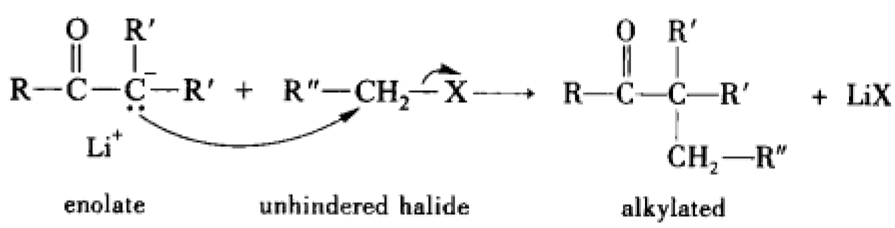
23-5 Alkylation of Enolate Ions

We have seen many reactions where nucleophiles attack unhindered alkyl halides and tosylates by the S_N2 mechanism. An enolate ion can serve as the nucleophile, becoming alkylated in the process. Because the enolate has two nucleophilic sites (the oxygen and the α carbon), it can react at either of these sites. The reaction usually takes place primarily at the α carbon, forming a new C—C bond. In effect, this is another type of α substitution, with an alkyl group substituting for an α hydrogen.

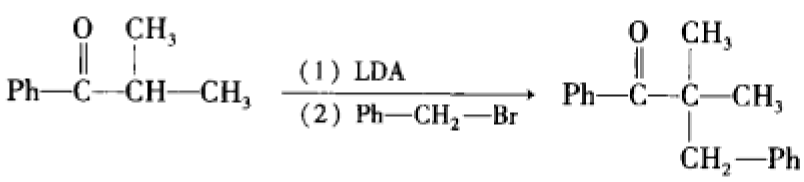


Typical bases such as sodium hydroxide or an alkoxide ion cannot be used to form enolates for alkylation because at equilibrium a large quantity of the hydroxide or alkoxide base is still present. These strongly nucleophilic bases give side reactions with the alkyl halide or tosylate. Lithium diisopropylamide (LDA) avoids these side reactions. Because it is a much stronger base, LDA converts the ketone entirely to its enolate. All the LDA is consumed in forming the enolate, leaving the enolate to react without interference from the LDA. Also, LDA is a very bulky base and thus a poor nucleophile, so it generally does not react with the alkyl halide or tosylate.





Example

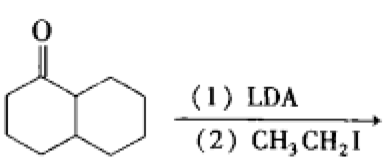


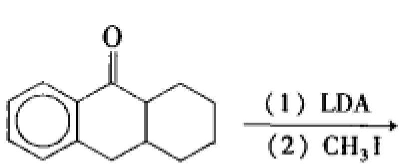
Direct alkylation of enolates (using LDA) gives the best yields when only one kind of α hydrogen can be replaced by an alkyl group. If there are two different kinds of α protons that may be abstracted to give enolates, mixtures of products alkylated at the different α carbons may result. Aldehydes are not suitable for direct alkylation because they undergo side reactions when treated with LDA.

PROBLEM 23-8

Predict the major products of the following reactions.

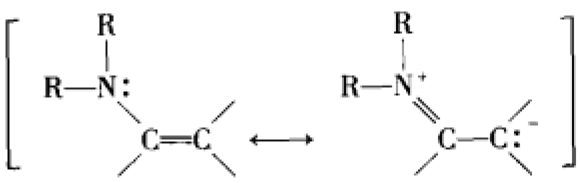
(a) acetone $\xrightarrow[\text{(2) } CH_2=CHCH_2Br]{\text{(1) LDA}}$

(b) 

(c) 

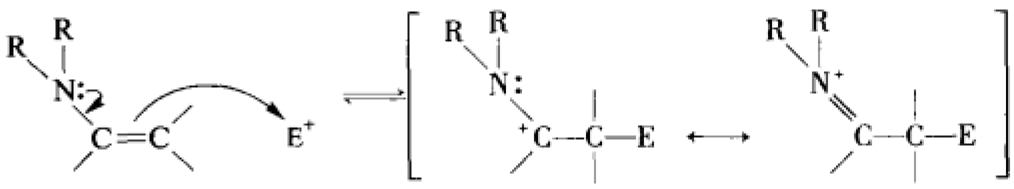
23-6 Formation and Alkylation of Enamines

A milder alternative to direct alkylation of enolate ions is the formation and alkylation of an enamine derivative. An **enamine** (a **vinyl amine**) is the nitrogen analogue of an enol. The resonance picture of an enamine shows that it has some carbanion character.



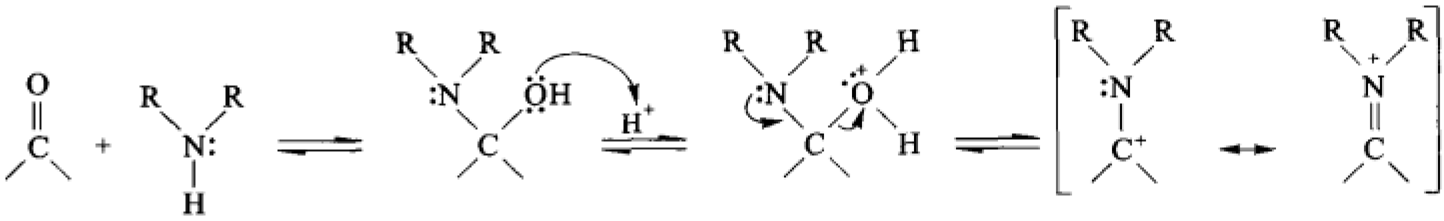
major minor

An enamine is a stronger nucleophile than an enol, but still quite selective in its alkylation reactions. The nucleophilic carbon atom attacks an electrophile to give a resonance-stabilized cationic intermediate (an iminium ion).

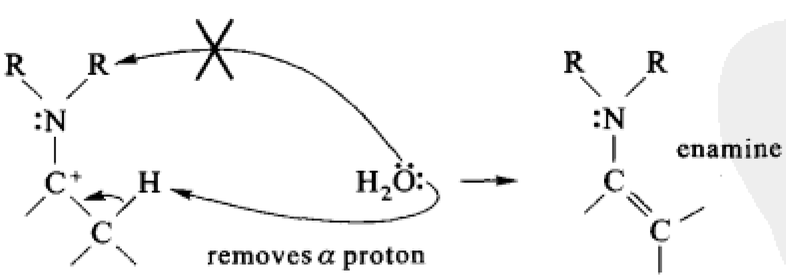


an enamine electrophile minor major

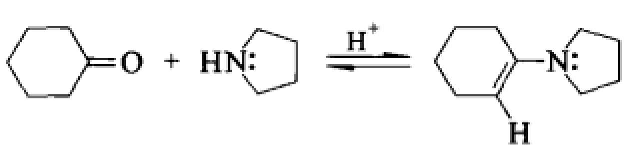
An enamine results from the reaction of a ketone or aldehyde with a secondary amine. Recall that a ketone or aldehyde reacts with a *primary* amine (Section 19-12) to form a carbinolamine, which dehydrates to give the C=N double bond of an imine. But a carbinolamine from a *secondary* amine does not form a C=N double bond because there is no proton on nitrogen to eliminate. A proton is lost from the α carbon, forming the C=C double bond of an enamine.



2° amine 2° carbinolamine(醇胺) no proton on N



Example

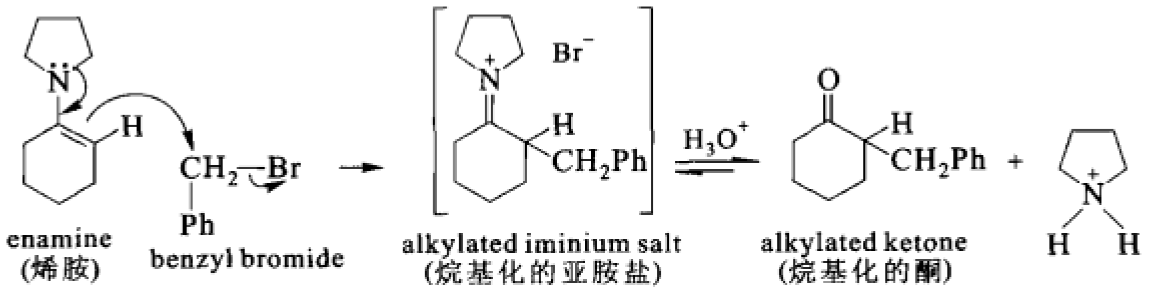


cyclohexanone pyrrolidine (四氢吡咯) pyrrolidine enamine of cyclohexanone (环己酮四氢吡咯烯胺)

PROBLEM 23-9

Propose a mechanism for the acid-catalyzed reaction of cyclohexanone with pyrrolidine.

Enamines displace halides from reactive alkyl halides, giving alkylated iminium salts. The iminium ions are unreactive toward further alkylation or acylation. The following example shows benzyl bromide reacting with the pyrrolidine enamine of cyclohexanone.



PROBLEM 23-10

Show how you would accomplish each conversion using an enamine synthesis.

(a) cyclopentanone ⟶ 2-allylcyclopentanone

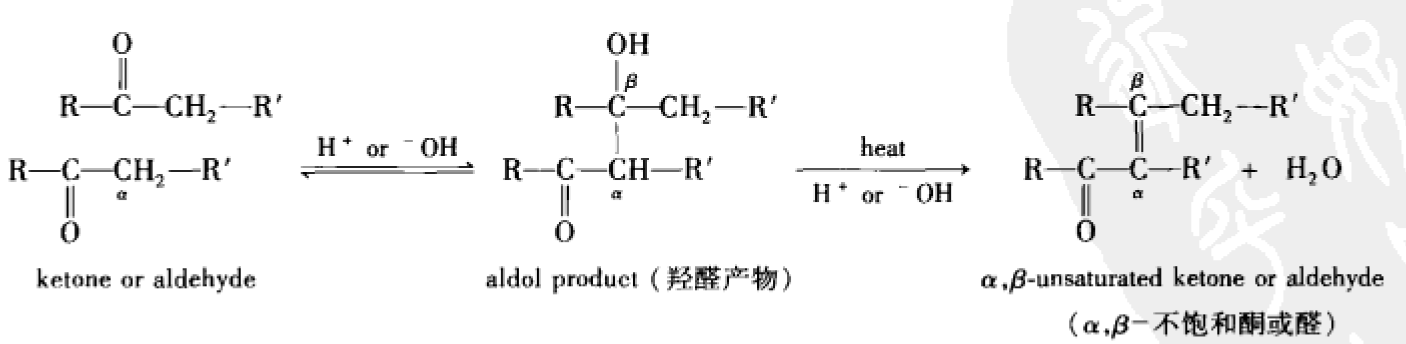
(b) 3-pentanone ⟶ 2-methyl-1-phenyl-3-pentanone

(c) acetophenone ⟶ $\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}Ph}$

23-7 The Aldol Condensation of Ketones and Aldehydes

Condensations are some of the most important enolate reactions of carbonyl compounds. Condensations combine two or more molecules, often with the loss of a small molecule such as water or an alcohol. Under basic conditions, the **aldol condensation** involves the nucleophilic addition of an enolate ion to another carbonyl group. The product, a β-hydroxy ketone or aldehyde, is called an **aldol** because it contains both an *ald*ehyde group and the hydroxy group of an alcoh*ol*. The aldol product may dehydrate to an α,β-unsaturated carbonyl compound.

The aldol condensation



23-7A Base-Catalyzed Aldol Condensations

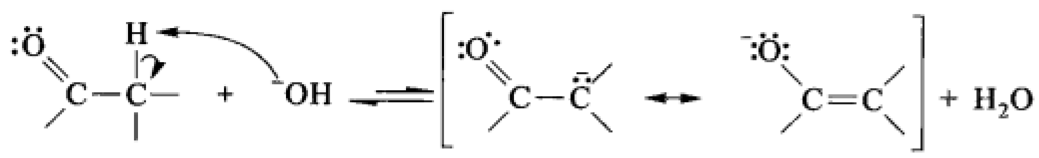
Under basic conditions, the aldol condensation occurs by a nucleophilic addition of the enolate ion (a strong nucleophile) to a carbonyl group. Protonation gives the aldol product. Note that the carbonyl group serves as the

electrophile that is attacked by the nucleophilic enolate ion. From the electrophile's viewpoint, the reaction is a nucleophilic addition across the carbonyl double bond. From the viewpoint of the enolate ion, the reaction is an alpha substitution: The other carbonyl compound replaces an alpha hydrogen.

KEY MECHANISM 23-9 Base-Catalyzed Aldol Condensation

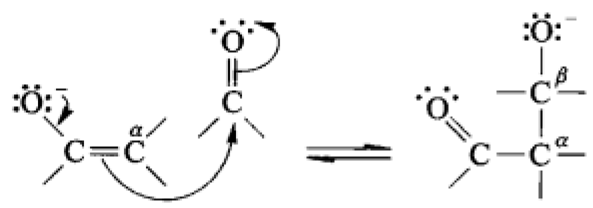
The base-catalyzed aldol involves the nucleophilic addition of an enolate ion to a carbonyl group.

Step 1: A base removes an α proton to form an enolate ion.



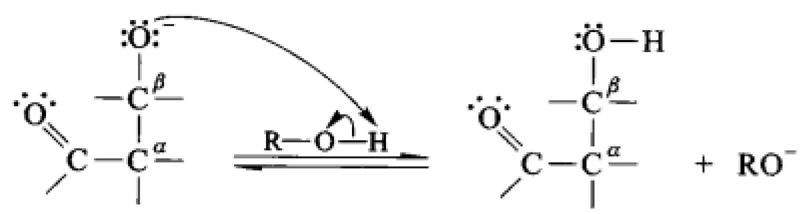
enolate ion

Step 2: The enolate ion adds to the carbonyl group.



enolate carbonyl alkoxide

Step 3: Protonation of the alkoxide gives the aldol product.

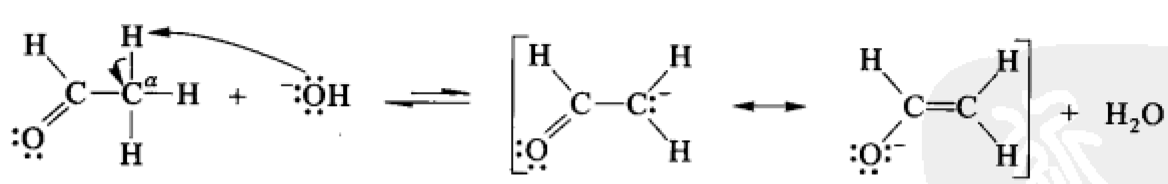


alkoxide aldol product

EXAMPLE: Aldol condensation of acetaldehyde.

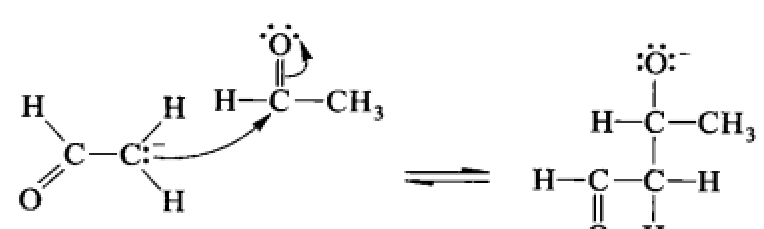
The enolate ion of acetaldehyde attacks the carbonyl group of another acetaldehyde molecule. Protonation gives the aldol product.

Step 1: A base removes an α proton to form an enolate ion.



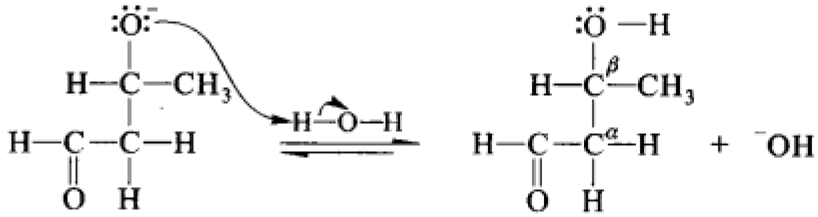
acetaldehyde (乙醛) base enolate of acetaldehyde

Step 2: The enolate ion adds to the carbonyl group.



enolate acetaldehyde

***Step 3*:** Protonation of the alkoxide gives the aldol product.



The aldol condensation is reversible, establishing an equilibrium between reactants and products. For acetaldehyde, conversion to the aldol product is about 50%. Ketones also undergo aldol condensation, but equilibrium concentrations of the products are generally small. Aldol condensations are sometimes accomplished by clever experimental methods. For example, Figure 23−2 shows how a good yield of the acetone aldol product ("diacetone alcohol") is obtained, even though the equilibrium concentration of the product is only about 1%. Acetone is boiled so it condenses into a chamber containing an insoluble basic catalyst. The reaction can take place only in the catalyst chamber. When the solution returns to the boiling flask, it contains about 1% diacetone alcohol. Diacetone alcohol is less volatile than acetone, remaining in the boiling flask while acetone boils and condenses (refluxes) in contact with the catalyst. After several hours, nearly all the acetone is converted to diacetone alcohol.

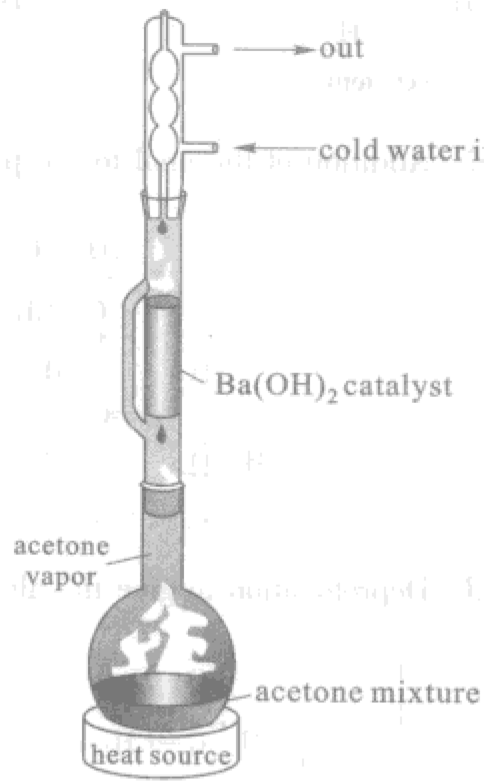
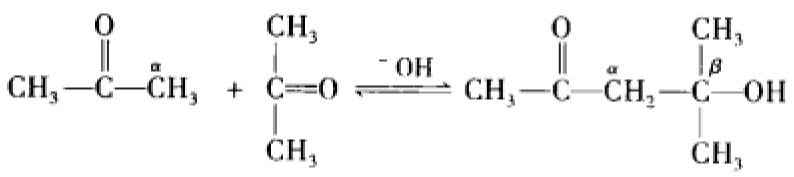


Figure 23−2 Driving an aldol condensation to completion.



2 acetone (丙酮)
(99%)

4-hydroxy-4-methyl-2-pentanone
"diacetone alcohol"
(1%)

PROBLEM 23−11

A student wanted to dry some diacetone alcohol and allowed it to stand over anhydrous potassium carbonate for a week. At the end of the week, the sample was found to contain nearly pure acetone. Propose a mechanism for the reaction that took place.

23−7B Acid-Catalyzed Aldol Condensations

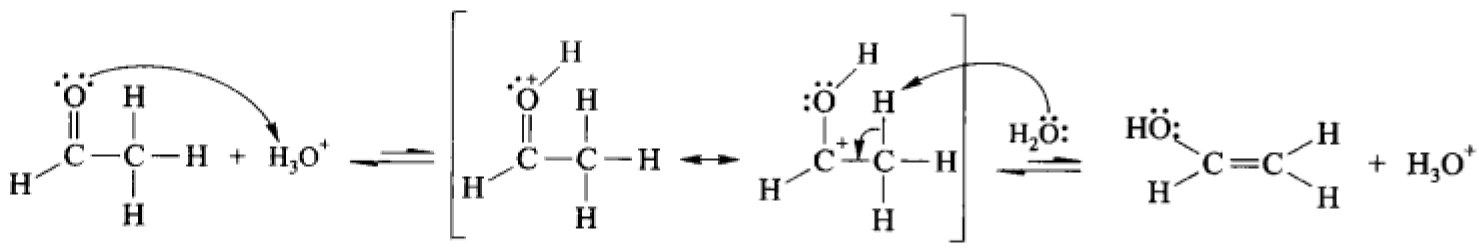
Aldol condensations also take place under acidic conditions. The enol serves as a weak nucleophile to attack an activated (protonated) carbonyl group. As an example, consider the acid-catalyzed aldol condensation of acetaldehyde. The first step is formation of the enol by the acid-catalyzed keto-enol tautomerism, as discussed earlier.

The enol attacks the protonated carbonyl of another acetaldehyde molecule. Loss of the enol proton gives the aldol product.

MECHANISM 23-10 **Acid-Catalyzed Aldol Condensation**

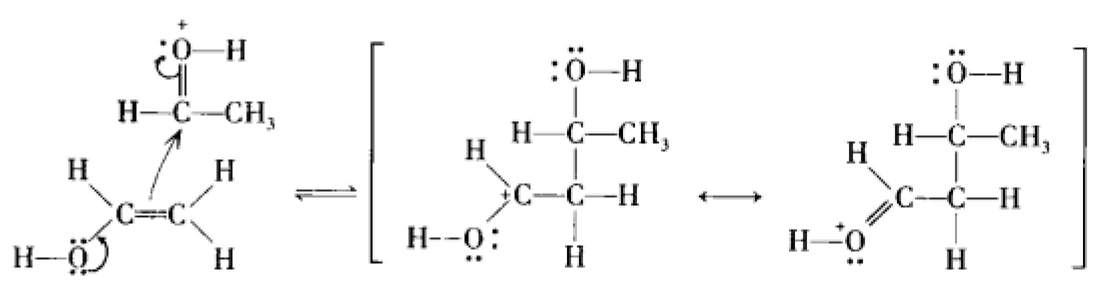
The acid-catalyzed aldol involves nucleophilic addition of an enol to a protonated carbonyl group.

***Step 1*:** Formation of the enol, by protonation on O followed by deprotonation on C.



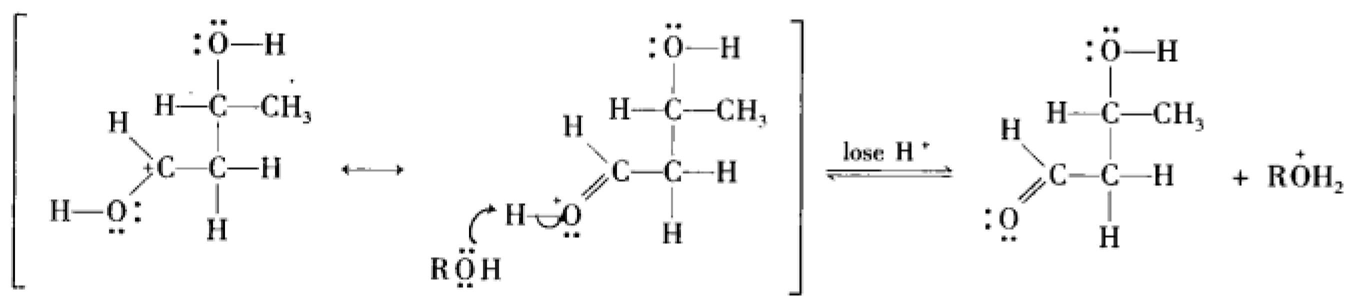
keto form   protonated carbonyl   enol form

***Step 2*:** Addition of the enol to the protonated carbonyl.



attack by enol   resonance-stabilized intermediate

***Step 3*:** Deprotonation to give the aldol product.



resonance-stabilized intermediate   aldol product

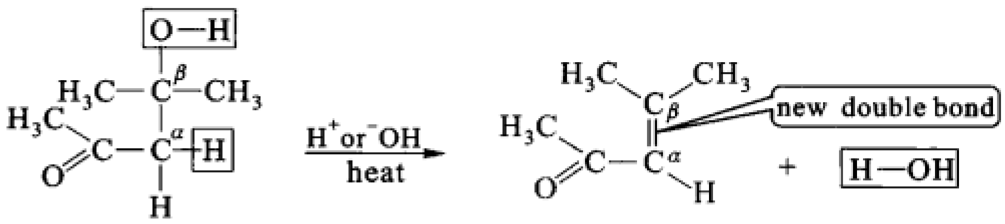
PROBLEM 23-12

Propose a complete mechanism for the acid-catalyzed aldol condensation of acetone.

23-8 Dehydration of Aldol Products

Heating a basic or acidic mixture of an aldol product leads to dehydration of the alcohol functional group. The product is a conjugated α,β-unsaturated aldehyde or ketone. Thus, an aldol condensation, followed by dehydration, forms a *new carbon-carbon double bond*. Before the Wittig reaction was discovered, the aldol with dehydration was probably the best method for joining two molecules with a double bond. It is still often the cheapest and

easiest method.



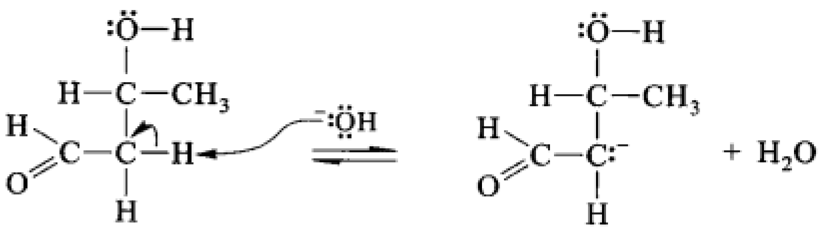
diacetone alcohol (双丙酮醇) 4-methyl-3-penten-2-one (mesityl oxide) (4-甲基-3-戊烯-2-酮)

Under acidic conditions, dehydration follows a mechanism similar to those of other acid-catalyzed alcohol dehydrations. We have not previously seen a base-catalyzed dehydration, however. Base-catalyzed dehydration depends on the acidity of the α proton of the aldol product. Abstraction of an α proton gives an enolate that can expel hydroxide ion to give a more stable product. Hydroxide is not a good leaving group in an E2 elimination, but it can serve as a leaving group in a strongly exothermic step like this one, which stabilizes a negatively charged intermediate. The following mechanism shows the base-catalyzed dehydration of 3-hydroxybutanal.

KEY MECHANISM 23-11 Base-Catalyzed Dehydration of an Aldol

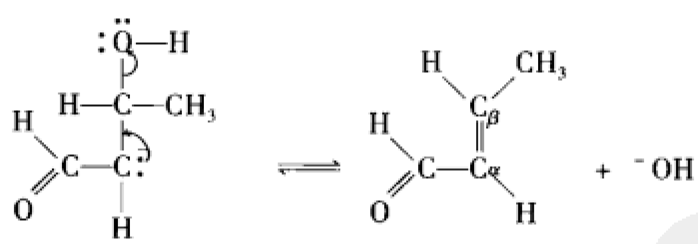
Unlike most alcohols, aldols undergo dehydration in base. Abstraction of an α proton gives an enolate that can expel hydroxide ion to give a conjugated product.

Step 1: Formation of the enolate ion.



removal of α proton resonance-stabilized enolate

Step 2: Elimination of hydroxide.



resonance stabilized enolate conjugated system (共轭体系)

Even when the aldol equilibrium is unfavorable for formation of a β-hydroxy ketone or aldehyde, the dehydration product may be obtained in good yield by heating the reaction mixture. Dehydration is usually exothermic because it leads to a conjugated system. In effect, the exothermic dehydration drives the aldol equilibrium to the right.

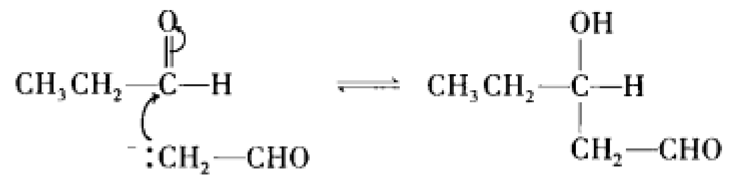
23-9 Crossed Aldol Condensations

When the enolate of one aldehyde (or ketone) adds to the carbonyl group of another, the result is called a **crossed aldol condensation.** The compounds used in the reaction must be selected carefully, or a mixture of

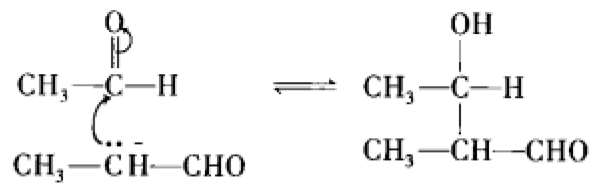
several products will be formed.

Consider the aldol condensation between acetaldehyde (ethanal) and propanal shown below. Either of these reagents can form an enolate ion. Attack by the enolate of ethanal on propanal gives a product different from the one formed by attack of the enolate of propanal on ethanal. Also, self-condensations of ethanal and propanal continue to take place. Depending on the reaction conditions, various proportions of the four possible products result.

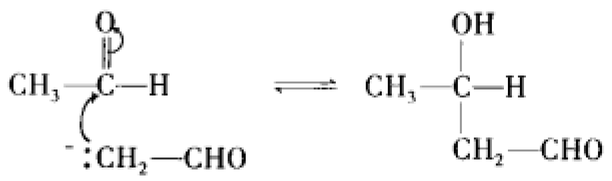
Enolate of ethanal adds to propanal



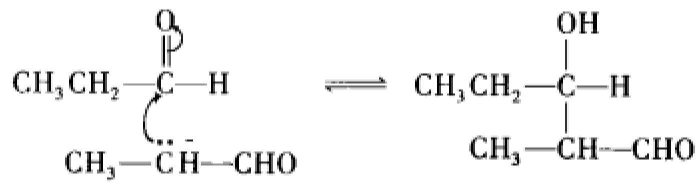
Enolate of propanal adds to ethanal



Self-condensation of ethanal

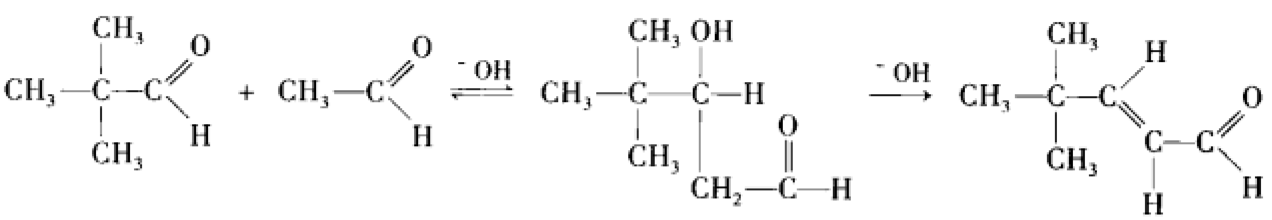


Self-condensation of propanal

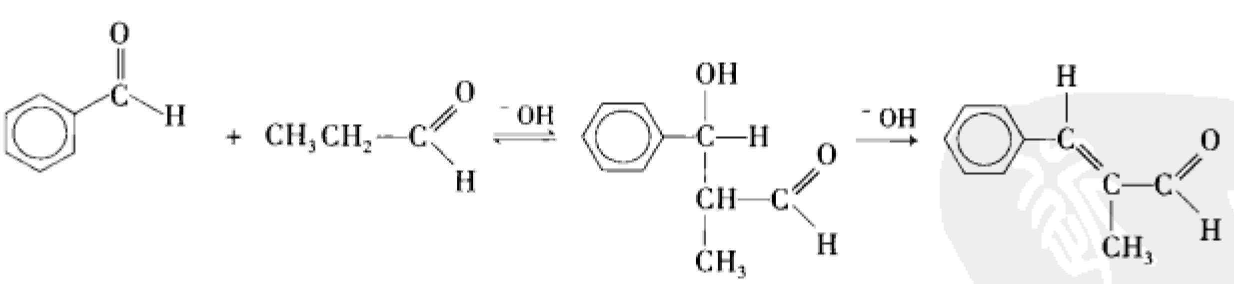


A crossed aldol condensation can be effective if it is planned so that only one of the reactants can form an enolate ion and so that the other compound is more likely to react with the enolate. If only one of the reactants has an α hydrogen, only one enolate will be present in the solution. If the other reactant is present in excess or contains a particularly electrophilic carbonyl group, it is more likely to be attacked by the enolate ion.

The following two reactions are successful crossed aldol condensations. The aldol products may or may not undergo dehydration, depending on the reaction conditions and the structure of the products.



excess, no α protons $\qquad$ α protons $\qquad$ aldol $\qquad$ dehydrated (75%)



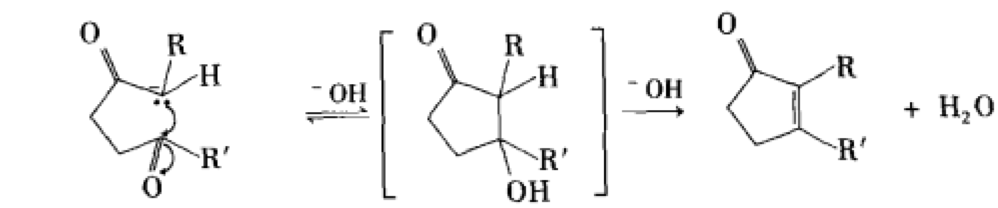
excess, no α protons $\qquad$ α protons $\qquad$ aldol $\qquad$ dehydrated (80%)

To carry out these reactions, slowly add the compound with α protons to a basic solution of the compound with no α protons. This way, the enolate ion is formed in the presence of a large excess of the other component, and the desired reaction is favored.

23-10 Aldol Cyclizations

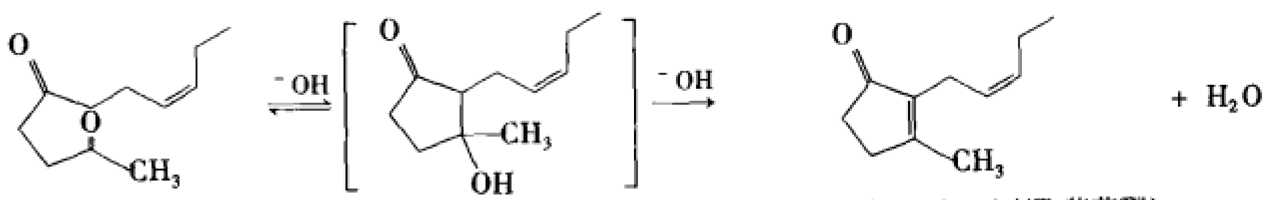
Intramolecular aldol reactions of diketones are often useful for making five- and six- membered rings. Aldol cycli-

zations of rings larger than six and smaller than five are less common because larger and smaller rings are less favored by their energy and entropy. The following reactions show how a 1,4-diketone can condense and dehydrate to give a cyclopentenone and how a 1,5-diketone gives a cyclohexenone.

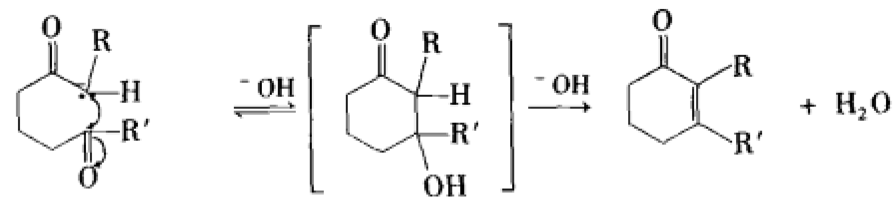


enolate of a 1,4-diketone   aldol product   a cyclopentenone

Example

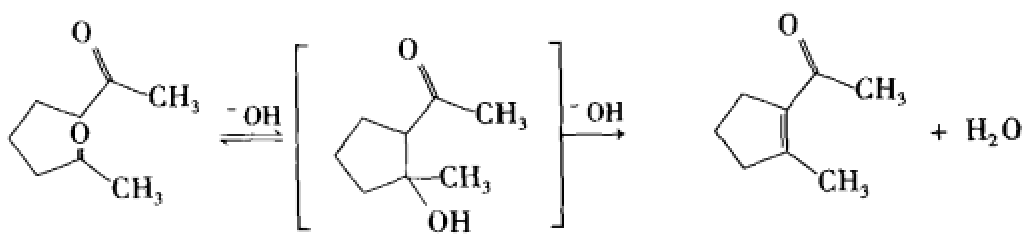


cis-8-undecene-2,5-dione   aldol product   *cis*-jasmone (a perfume)(顺-茉莉酮) (90%)



enolate of a 1,5-diketone   aldol product   a cyclohexenone

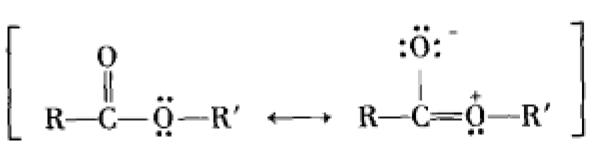
The following example shows how the carbonyl group of the product may be outside the ring in some cases.



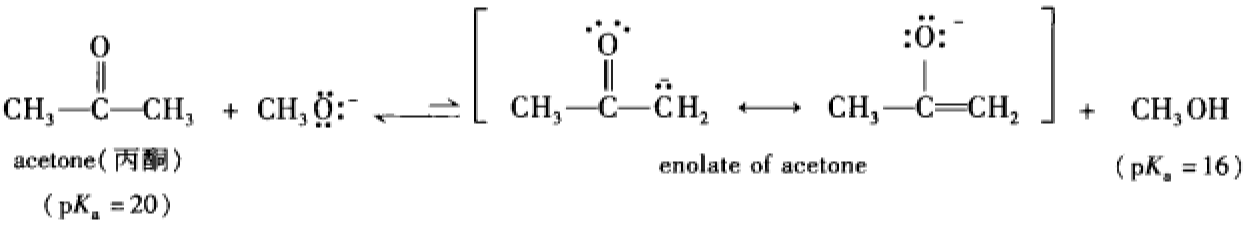
2,7-octanedione   aldol product   1-acetyl-2-methylcyclopentene

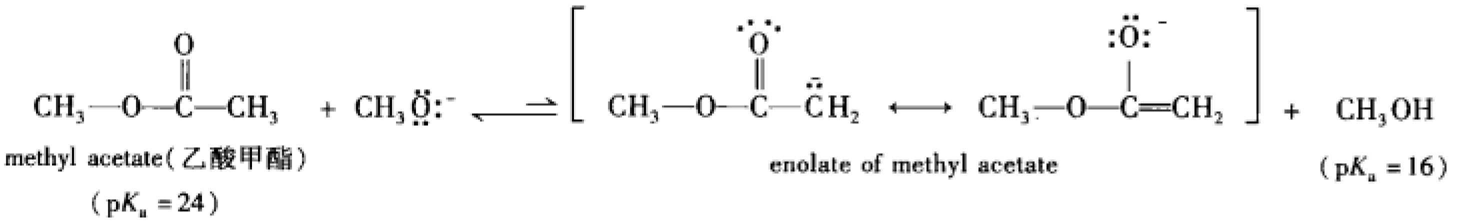
23-11 The Claisen Ester Condensation

The α hydrogens of esters are weakly acidic, and they can be deprotonated to give enolate ions. Esters are less acidic than ketones and aldehydes because the ester carbonyl group is stabilized by resonance with the other oxygen atom. This resonance makes the carbonyl group less capable of stabilizing the negative charge of an enolate ion.



A typical pK_a for an α proton of an ester is about 24, compared with a pK_a of about 20 for a ketone or aldehyde. Even so, strong bases do deprotonate esters.





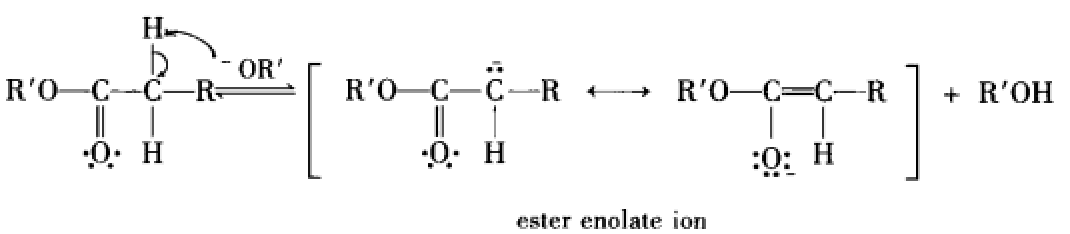
Ester enolates are strong nucleophiles, and they undergo a wide range of interesting and useful reactions. Most of these reactions are related to the Claisen condensation, the most important of all ester condensations.

The **Claisen condensation** results when an ester molecule undergoes nucleophilic acyl substitution by an enolate. The intermediate has an alkoxy (—OR) group that acts as a leaving group, leaving a β-keto ester. The overall reaction combines two ester molecules to give a β-keto ester.

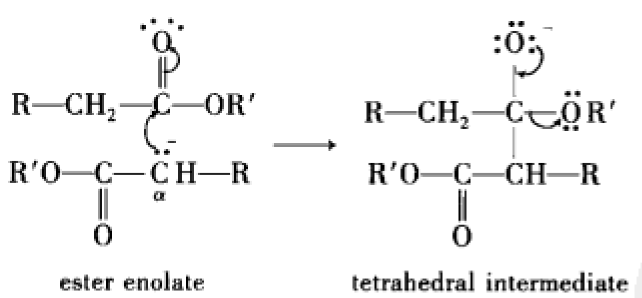
KEY MECHANISM 23-12 The Claisen Ester Condensation

The Claisen condensation is a nucleophilic acyl substitution on an ester, in which the attacking nucleophile is an enolate ion.

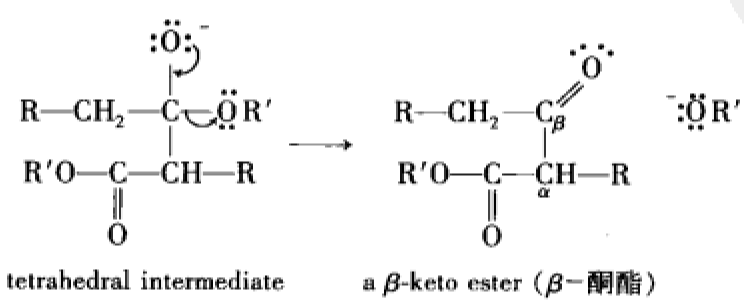
Step 1: Formation of the enolate ion.



Step 2: Addition of the enolate to give a tetrahedral intermediate.

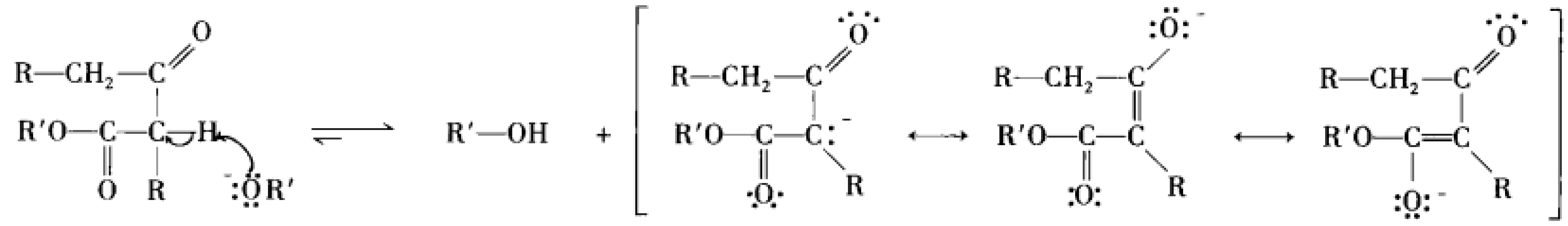


Step 3: Elimination of the alkoxide leaving group.



Notice that one molecule of the ester (deprotonated, reacting as the enolate) serves as the nucleophile to attack another molecule of the ester, which serves as the acylating reagent in this nucleophilic acyl substitution.

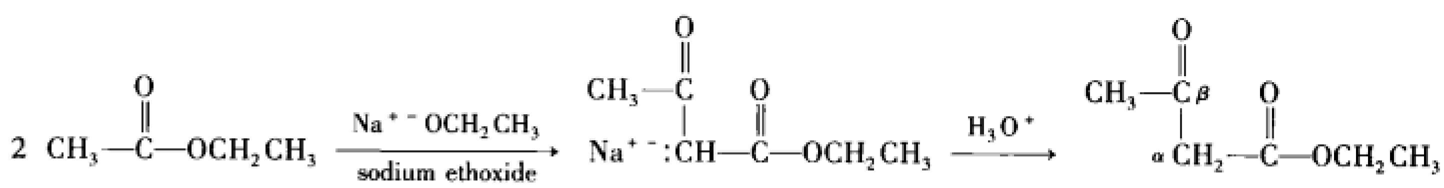
The β-keto ester products of Claisen condensations are more acidic than simple ketones, aldehydes, and esters because the negative charge of the enolate is delocalized over both carbonyl groups. β-Keto esters have pK_a values around 11, showing they are stronger acids than water. In strong base such as ethoxide ion or hydroxide ion, the β-keto ester is rapidly and completely deprotonated.



a β-keto ester ($pK_a = 11$) — ($pK_a = 16-18$) — resonance-stabilized enolate ion

Deprotonation of the β-keto ester provides a driving force for the Claisen condensation. The deprotonation is strongly exothermic, making the overall reaction exothermic and driving the reaction to completion. Because the base is consumed in the deprotonation step, a full equivalent of base must be used, and the Claisen condensation is said to be *base-promoted* rather than *base-catalyzed*. After the reaction is complete, addition of dilute acid converts the enolate back to the β-keto ester.

The following example shows the self-condensation of ethyl acetate to give ethyl acetoacetate (ethyl 3-oxobutanoate). Ethoxide is used as the base to avoid transesterification or hydrolysis of the ethyl ester. The initial product is the enolate of ethyl acetoacetate, which is reprotonated in the final step.



ethyl acetate — keto ester enolate — ethyl acetoacetate (75%)
(乙酰乙酸乙酯)

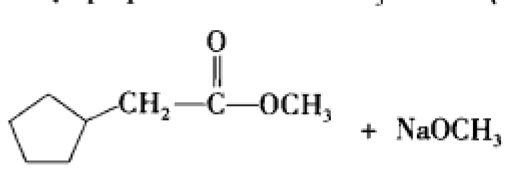
PROBLEM 23-13

Esters with only one α hydrogen generally give poor yields in the Claisen condensation. Propose a mechanism for the Claisen condensation of ethyl isobutyrate, and explain why a poor yield is obtained.

PROBLEM 23-14

Predict the products of self-condensation of the following esters.

(a) methyl propanoate + $NaOCH_3$ (b) ethyl phenylacetate + $NaOCH_2CH_3$

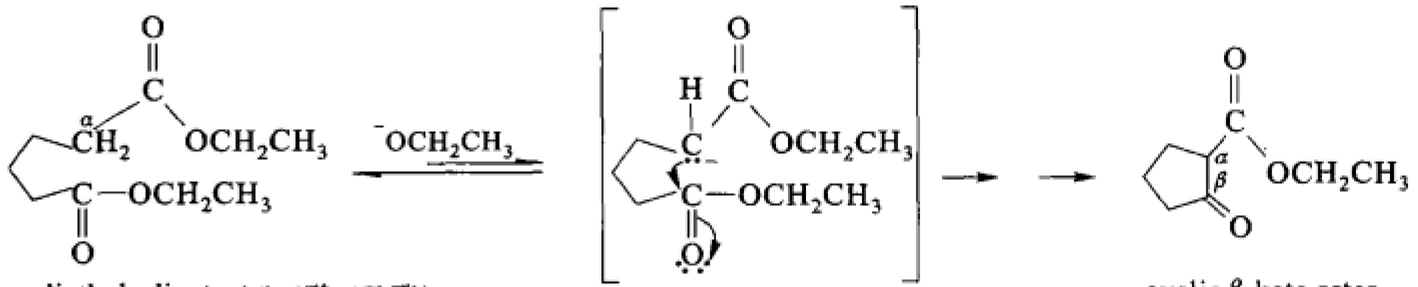
(c) 

23-12 The Dieckmann Condensation: A Claisen Cyclization

An internal Claisen condensation of a diester forms a ring. Such an internal Claisen cyclization is called a **Dieck-**

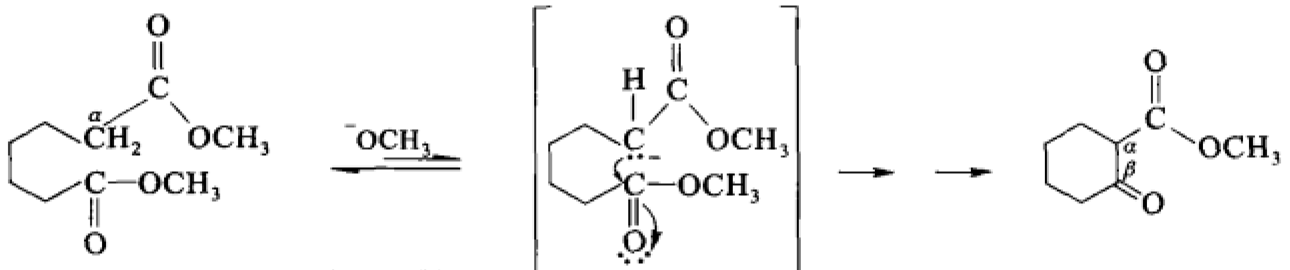
mann condensation or a **Dieckmann cyclization.** Five- and six-membered rings are easily formed by Dieckmann condensations. Rings smaller than five carbons or larger than six carbons are rarely formed by this method.

The following examples of the Dieckmann condensation show that a 1,6-diester gives a five-membered ring, and a 1,7-diester gives a six-membered ring.



diethyl adipate (己二酸二乙酯)
(a 1,6-diester)

cyclic β-keto ester
(80%)



dimethyl pimelate (庚二酸二甲酯)
(a 1,7-diester)

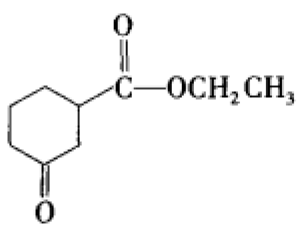
cyclic β-keto ester

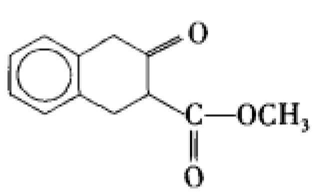
PROBLEM 23-15

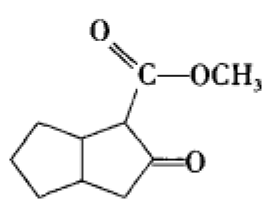
Propose mechanisms for the two Dieckmann condensations just shown.

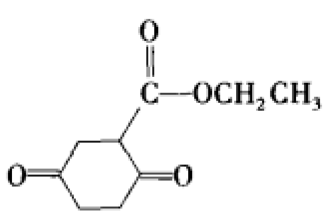
PROBLEM 23-16

Some (but not all) of the following keto esters can be formed by Dieckmann condensations. Determine which ones are possible, and draw the starting diesters.

(a) 

(b) 

(c) 

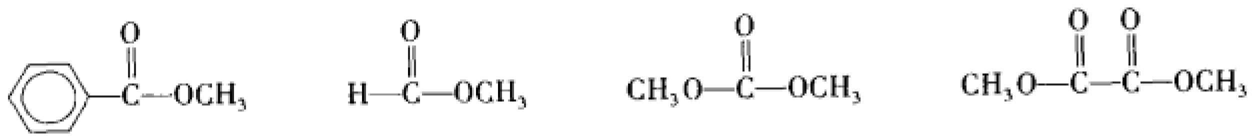
(d) 

(*Hint*: Consider using a protecting group.)

23-13 Crossed Claisen Condensations

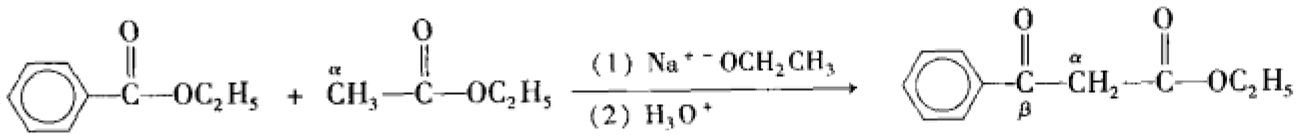
Claisen condensations can take place between different esters, particularly when only one of the esters has the α hydrogens needed to form an enolate. In a **crossed Claisen condensation**, an ester without α hydrogens serves

as the electrophilic component. Some useful esters without α hydrogens are benzoate, formate, carbonate, and oxalate esters.



methyl benzoate (苯甲酸甲酯) | methyl formate (甲酸甲酯) | dimethyl carbonate (碳酸二甲酯) | dimethyl oxalate (草酸二甲酯)

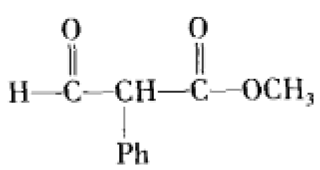
A crossed Claisen condensation is carried out by first adding the ester without α hydrogens to a solution of the alkoxide base. The ester with α hydrogens is slowly added to this solution, where it forms an enolate and condenses. The condensation of ethyl acetate with ethyl benzoate is an example of a crossed Claisen condensation.



ethyl benzoate (no α hydrogens) | ethyl acetate (forms enolate) | ethyl benzoylacetate (苯甲酰乙酸乙酯)

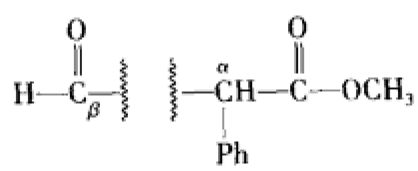
SOLVED PROBLEM 23-1

Show how a crossed Claisen condensation might be used to prepare

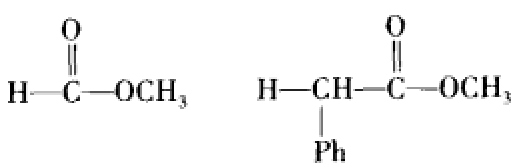


SOLUTION

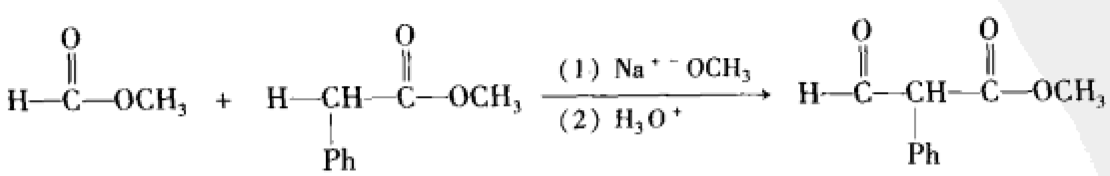
Break the α,β bond of this β-keto ester, since that is the bond formed in the Claisen condensation.



Now add the alkoxy group to the carbonyl and replace the proton on the α carbon.



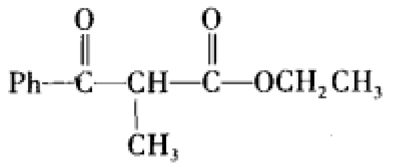
Write out the reaction, making sure that one of the components has α hydrogens and the other does not.

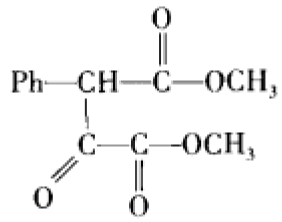


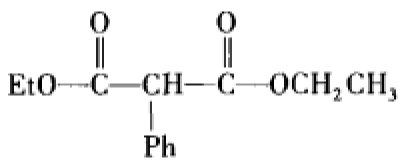
no α hydrogens | forms enolate

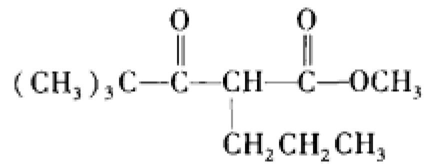
PROBLEM 23−17

Show how crossed Claisen condensations could be used to prepare the following esters.

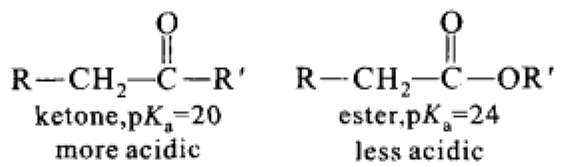
(a) 

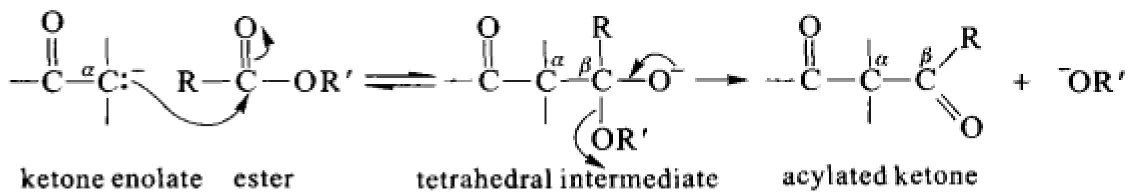
(b) 

(c) 

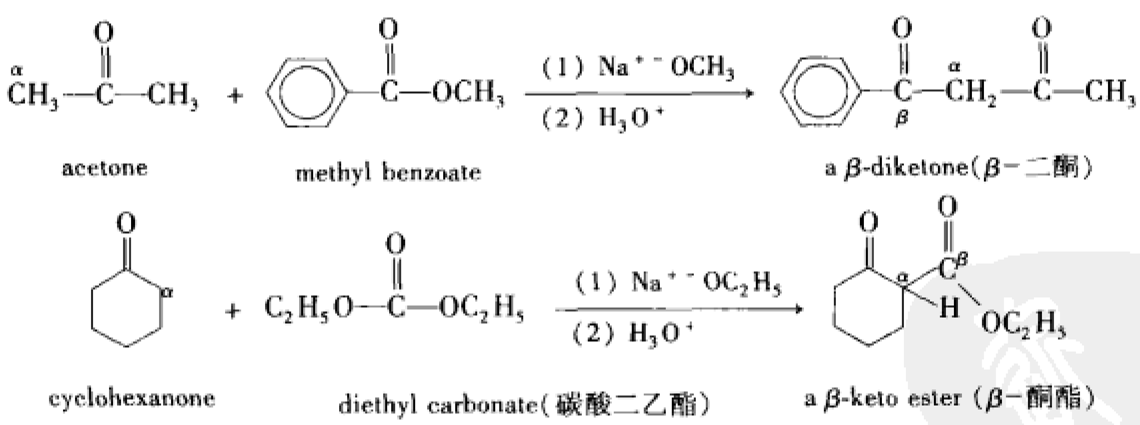
(d) 

Crossed Claisen condensations between ketones and esters are also possible. Ketones are more acidic than esters, and the ketone component is more likely to deprotonate and serve as the enolate component in the condensation. The ketone enolate attacks the ester, which undergoes nucleophilic acyl substitution and thereby acylates the ketone.



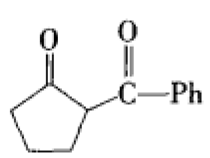


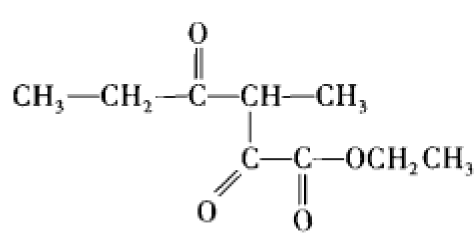
This condensation works best if the ester has no α hydrogens, so that it cannot form an enolate. Because of the difference in acidities, however, the reaction is often successful between ketones and esters even when both have α hydrogens. The following examples show some crossed Claisen condensations between ketones and esters. Notice the variety of difunctional and trifunctional compounds that can be produced by appropriate choices of esters.

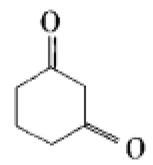


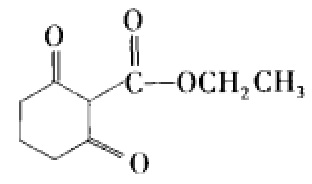
PROBLEM 23−18

Show how Claisen condensations could be used to make the following compounds.

(a) 

(b) 

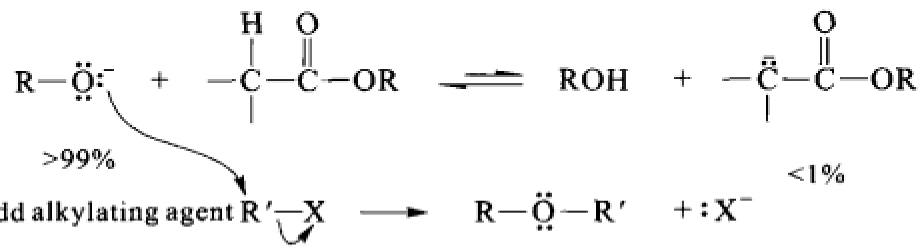
(c) 

(d) 

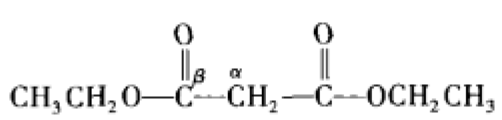
23－14 Syntheses Using *β*-Dicarbonyl Compounds

Many alkylation and acylation reactions are most effective using anions of *β*-dicarbonyl compounds that can be completely deprotonated and converted to their enolate ions by common bases such as methoxide ion and ethoxide ion. The *malonic ester synthesis* and the *acetoacetic ester synthesis* use the enhanced acidity of the α protons in malonic ester and acetoacetic ester to accomplish alkylations and acylations that are difficult or impossible with simple esters.

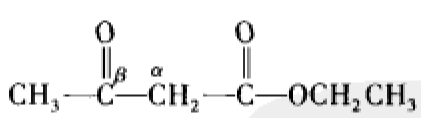
We have seen that most ester condensations use alkoxides to form enolate ions. With simple esters, only a small amount of enolate is formed; the equilibrium favors the alkoxide and the ester. The alkoxide often interferes with the desired reaction. For example, if we want an alkyl halide to alkylate an enolate, alkoxide ion in the solution will attack the alkyl halide and form an ether.



In contrast, *β*-dicarbonyl compounds, such as malonic ester and acetoacetic ester, are more acidic than alcohols. They are completely deprotonated by alkoxides, and the resulting enolates are easily alkylated and acylated. At the end of the synthesis, one of the carbonyl groups can be removed by decarboxylation, leaving a compound that is difficult or impossible to make by direct alkylation or acylation of a simple ester.



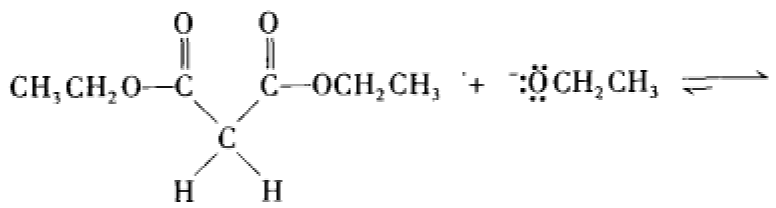
diethyl malonate (malonic ester)
(丙二酸二乙酯)



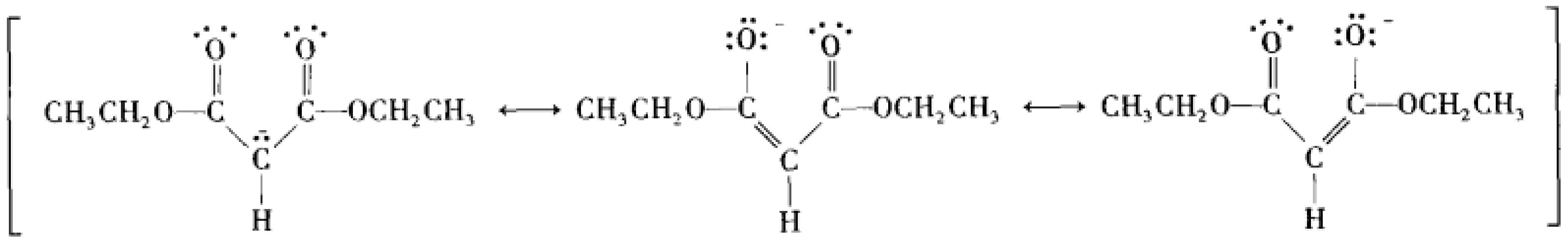
ethyl acetoacetate (acetoacetic ester)
(乙酰乙酸乙酯)

First we compare the acidity advantages of *β*-dicarbonyl compounds, and then we consider how these compounds are used in synthesis.

Acidities of *β*-Dicarbonyl Compounds Table 23－1 compares the acidities of some carbonyl compounds with the acidities of alcohols and water. Notice the large increase in acidity for compounds with two carbonyl groups beta to each other. The α protons of the *β*-dicarbonyl compounds are more acidic than the hydroxyl protons of water and alcohols. This enhanced acidity results from increased stability of the enolate ion. The negative charge is delocalized over two carbonyl groups rather than just one, as shown by the resonance forms for the enolate ion of diethyl malonate (also called *malonic ester*).



diethyl malonate (malonic ester)
($pK_a = 13$)



resonance-stabilized enolate ion

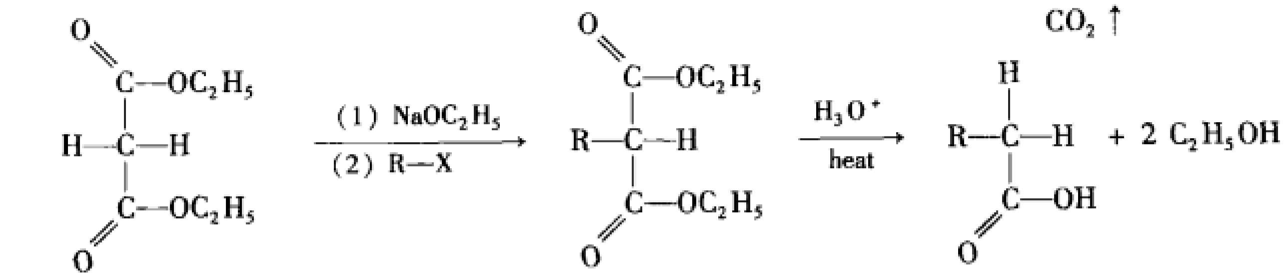
TABLE 23-1 Typical Acidities of Carbonyl Compounds

Conjugate Acid	Conjugate Base	pK_a
Simple ketones and esters		
$\overset{\alpha}{CH_3}$—C(=O)—CH_3 acetone	$^-:CH_2$—C(=O)—CH_3	20
$\overset{\alpha}{CH_3}$—C(=O)—OCH_2CH_3 ethyl acetate	$^-:CH_2$—C(=O)—OCH_2CH_3	24
β-dicarbonyl compounds		
CH_3—C(=O)$_\beta$—$\overset{\alpha}{CH_2}$—C(=O)—OCH_2CH_3 ethyl acetoacetate (acetoacetic ester)	CH_3—C(=O)—$\ddot{C}H$—C(=O)—OCH_2CH_3	11
CH_3CH_2O—C(=O)$_\beta$—$\overset{\alpha}{CH_2}$—C(=O)—OCH_2CH_3 diethyl malonate (malonic ester)	CH_3CH_2O—C(=O)—$\ddot{C}H$—C(=O)—OCH_2CH_3	13
Commonly used bases (for comparison)		
H—O—H water	^-OH	15.7
CH_3O—H methanol	CH_3O^-	15.5
CH_3CH_2O—H ethanol	$CH_3CH_2O^-$	15.9

23-15 The Malonic Ester Synthesis

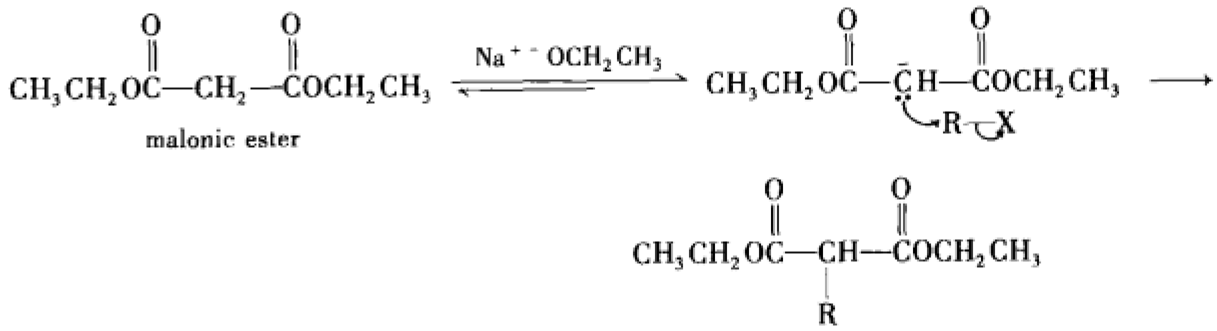
The **malonic ester synthesis** makes substituted derivatives of acetic acid. Malonic ester (diethyl malonate) is alkylated or acylated on the carbon that is α to both carbonyl groups, and the resulting derivative is hydrolyzed and allowed to decarboxylate.

Malonic ester synthesis



malonic ester (丙二酸酯) alkylated malonic ester (烷基化的丙二酸酯) substituted acetic acid (取代的乙酸)

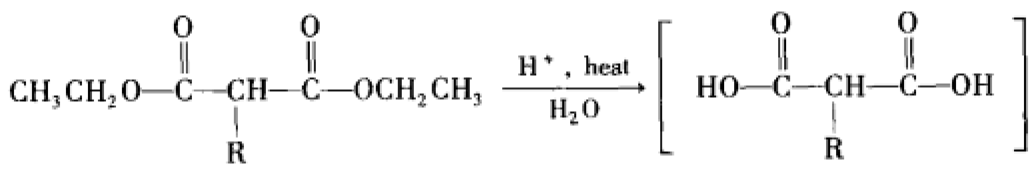
Malonic ester is completely deprotonated by sodium ethoxide. The resulting enolate ion is alkylated by an unhindered alkyl halide, tosylate, or other electrophilic reagent. This step is an S_N2 displacement, requiring a good S_N2 substrate.



malonic ester

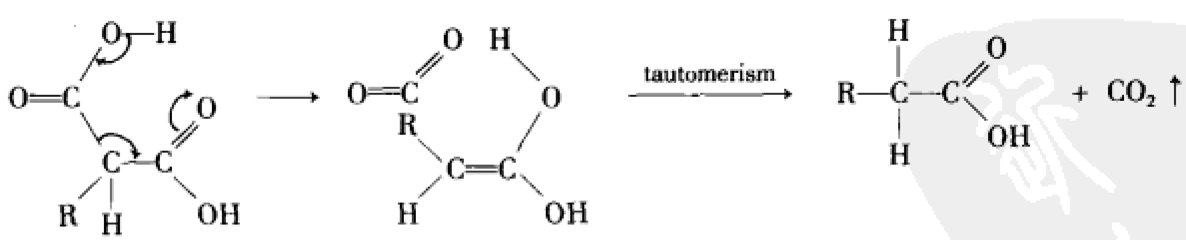
alkylated diethyl malonate

Hydrolysis of the alkylated diethyl malonate (a diethyl alkylmalonic ester) gives a malonic acid derivative.



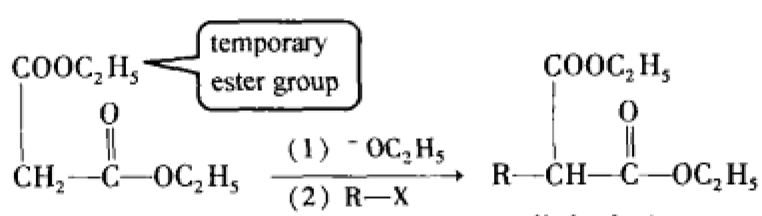
a diethyl alkylmalonate an alkylmalonic acid

Any carboxylic acid with a carbonyl group in the β position is prone to decarboxylate. At the temperature of the hydrolysis, the alkylmalonic acid loses CO_2 to give a substituted derivative of acetic acid. Decarboxylation takes place through a cyclic transition state, initially giving an enol that quickly tautomerizes to the product.

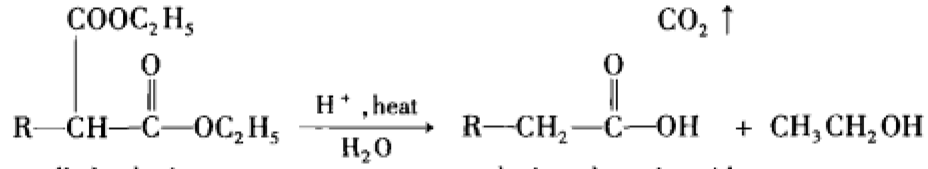


alkylmalonic acid CO_2 + enol substituted acetic acid

The product of a malonic ester synthesis is a substituted acetic acid, with the substituent being the group used to alkylate malonic ester. In effect, the second carboxyl group is temporary, allowing the ester to be easily deprotonated and alkylated. Hydrolysis with decarboxylation removes the temporary carboxyl group, leaving the substituted acetic acid.

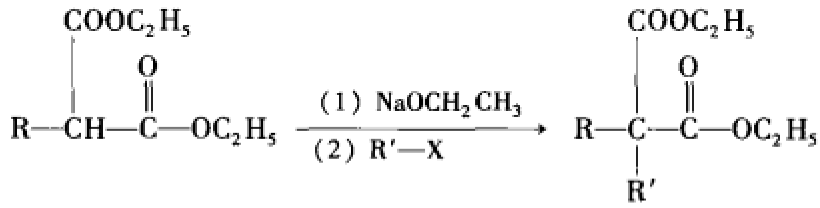


malonic ester alkylmalonic ester

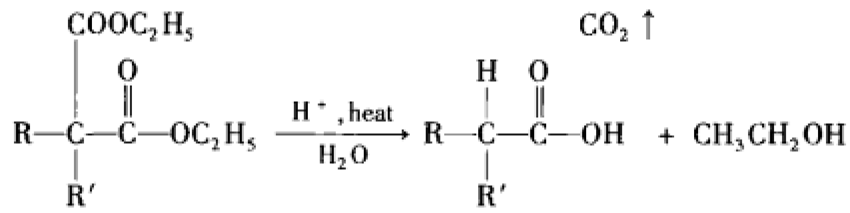


alkylmalonic ester — substituted acetic acid

The alkylmalonic ester has a second acidic proton that can be removed by a base. Removing this proton and alkylating the enolate with another alkyl halide gives a dialkylated malonic ester. Hydrolysis and decarboxylation leads to a disubstituted derivative of acetic acid.

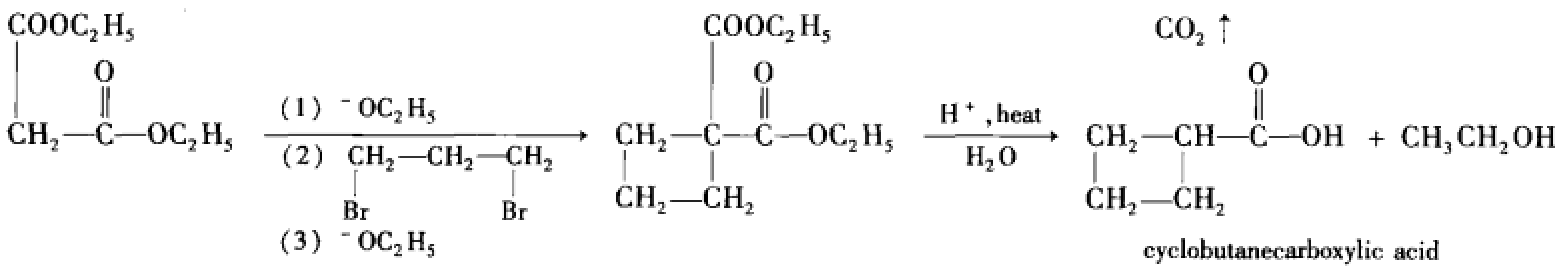


alkylmalonic ester — dialkylmalonic ester（二烷基化丙二酸酯）



dialkylmalonic ester — disubstituted acetic acid（二取代乙酸）

The malonic ester synthesis is useful for making cycloalkanecarboxylic acids, some of which are not easily made by any other method. The ring is formed from a dihalide, using a double alkylation of malonic ester. The following synthesis of cyclobutanecarboxylic acid shows that a strained four-membered ring system can be generated by this ester alkylation, even though most other condensations cannot form four-membered rings.



cyclobutanecarboxylic acid
（环丁烷羧酸）

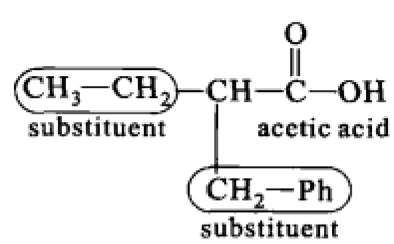
The malonic ester synthesis might seem like an arcane technique that only an organic chemist would use. Still, it is much like the method that cells use to synthesize the long-chain fatty acids found in fats, oils, waxes, and cell membranes.

SOLVED PROBLEM 23-2

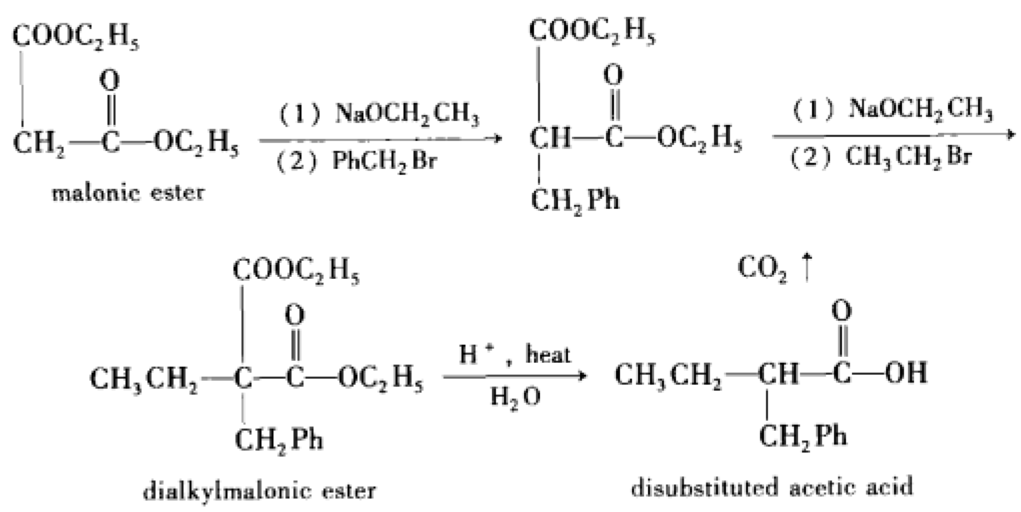
Show how the malonic ester synthesis is used to prepare 2-benzylbutanoic acid.

SOLUTION

2-Benzylbutanoic acid is a substituted acetic acid having the substituents Ph—CH_2— and CH_3CH_2—.



Adding these substituents to the enolate of malonic ester eventually gives the correct product.



PROBLEM 23-19

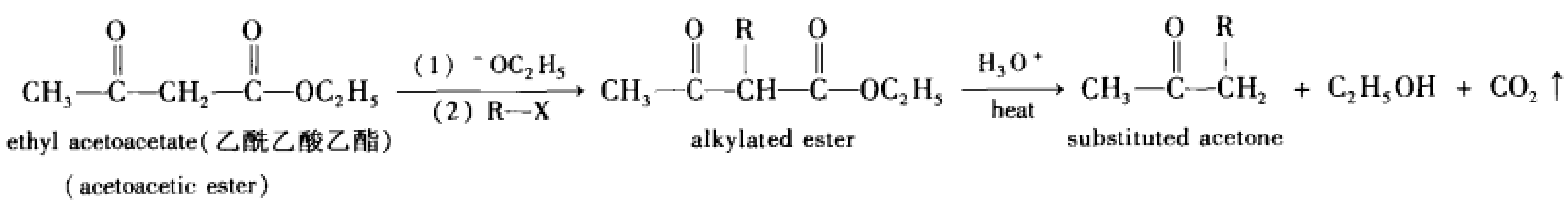
Show how the following compounds can be made using the malonic ester synthesis.

(a) 3-phenylpropanoic acid **(b)** 2-methylpropanoic acid

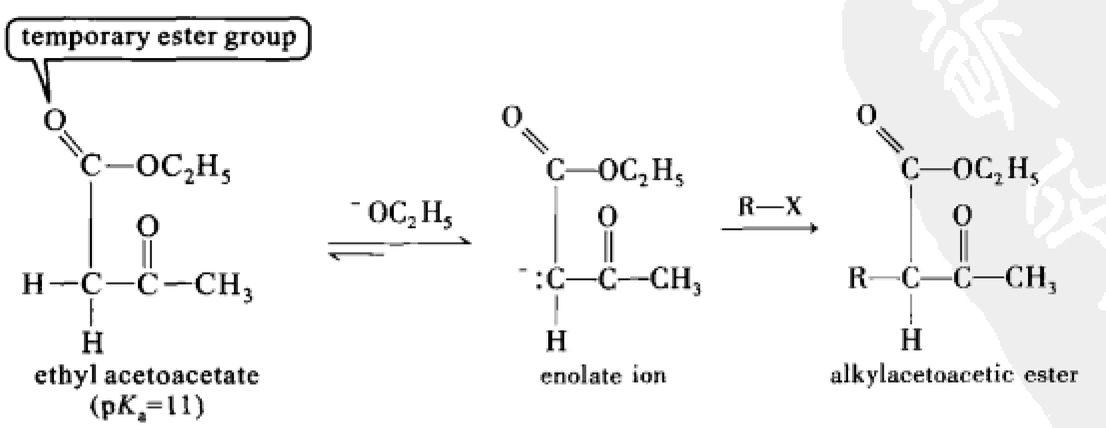
(c) 4-phenylbutanoic acid **(d)** cyclopentanecarboxylic acid

23-16 The Acetoacetic Ester Synthesis

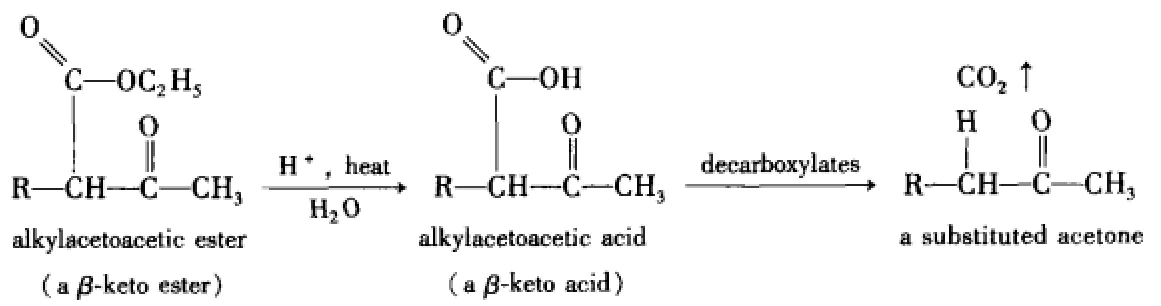
The **acetoacetic ester synthesis** is similar to the malonic ester synthesis, but the final products are ketones: specifically, substituted derivatives of acetone. In the acetoacetic ester synthesis, substituents are added to ethyl acetoacetate (acetoacetic ester), followed by hydrolysis and decarboxylation to produce an alkylated derivative of acetone.



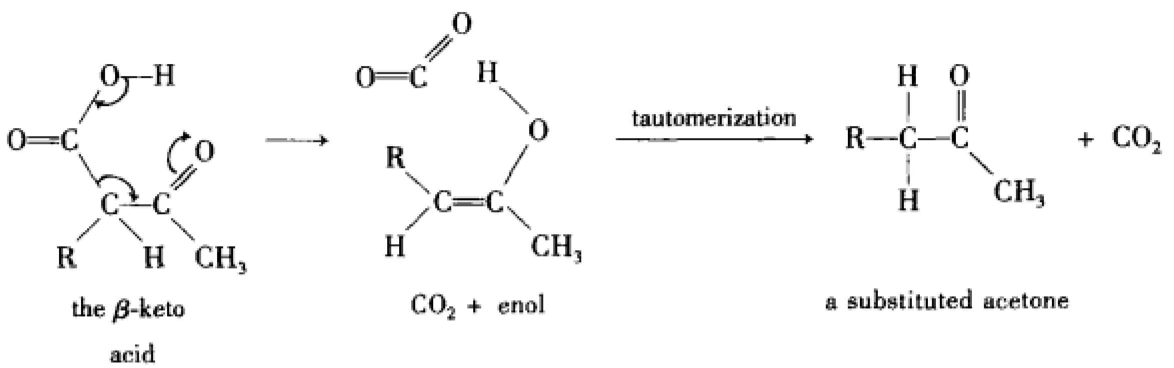
Acetoacetic ester is like a molecule of acetone with a temporary ester group attached to enhance its acidity. Ethoxide ion completely deprotonates acetoacetic ester. The resulting enolate is alkylated by an unhindered alkyl halide or tosylate to give an alkylacetoacetic ester. One again, the alkylating agent must be a good S_N2 substrate.



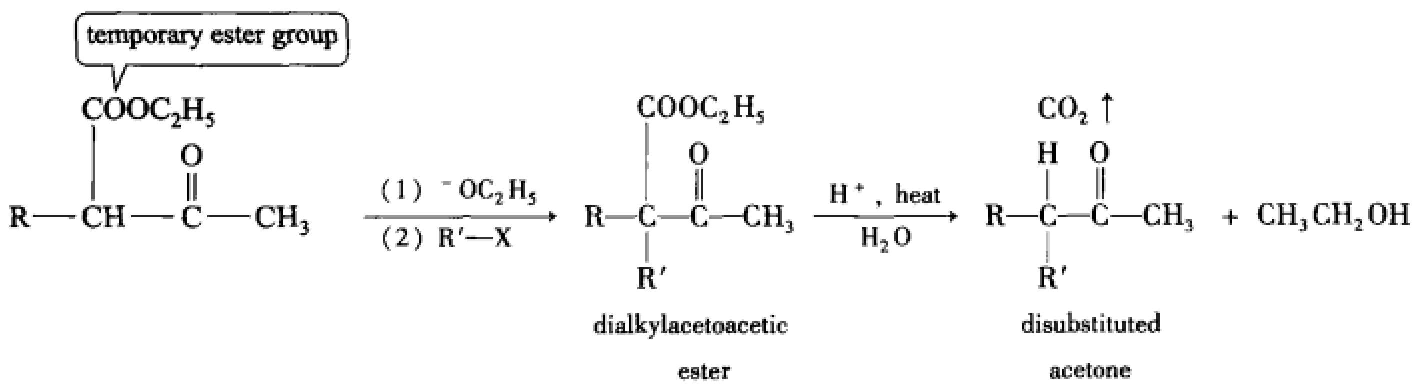
Acidic hydrolysis of the alkylacetoacetic ester initially gives an alkylacetoacetic acid, which is a β-keto acid. The keto group in the β position promotes decarboxylation to form a substituted version of acetone.



The β-keto acid decarboxylates by the same mechanism as the alkylmalonic acid in the malonic ester synthesis. A six-membered cyclic transition state splits out carbon dioxide to give the enol form of the substituted acetone. This decarboxylation usually takes place spontaneously at the temperature of the hydrolysis.



Disubstituted acetones are formed simply by alkylating acetoacetic ester a second time before the hydrolysis and decarboxylation steps, as shown in the following general synthesis.

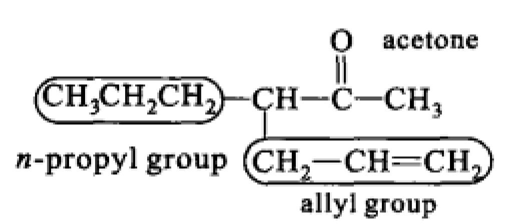


SOLVED PROBLEM 23-3

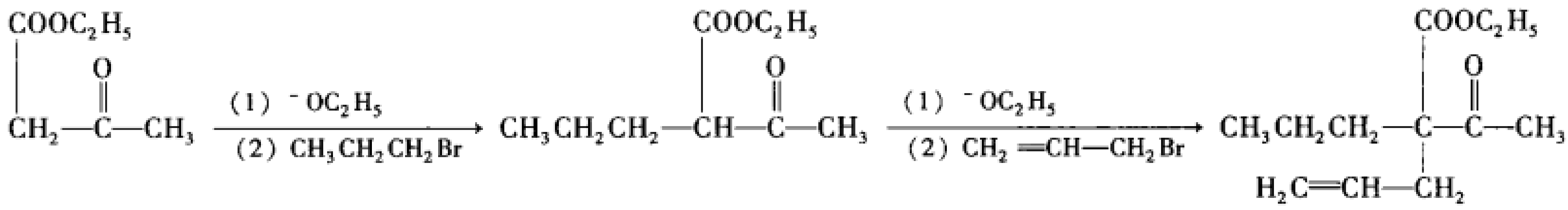
Show how the acetoacetic ester synthesis is used to make 3-propylhex-5-en-2-one.

SOLUTION

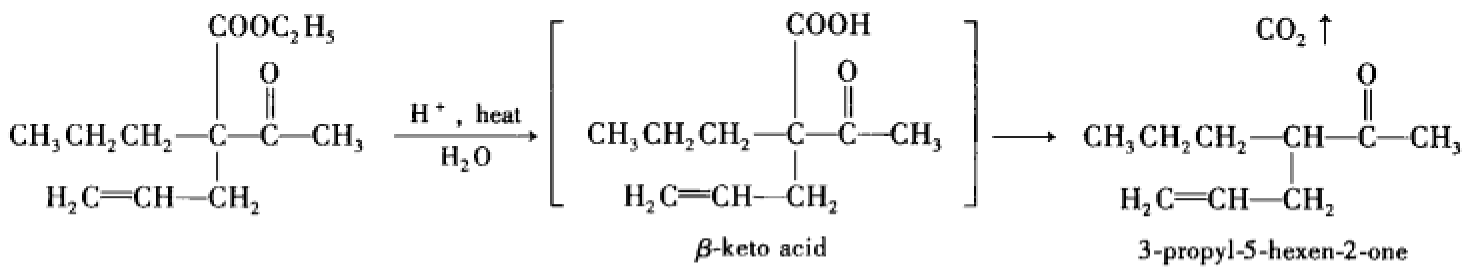
The target compound is acetone with an *n*-propyl group and an allyl group as substituents:



With an *n*-propyl halide and an allyl halide as the alkylating agents, the acetoacetic ester synthesis should produce 3-propyl-5-hexen-2-one. Two alkylation steps give the required substitution:

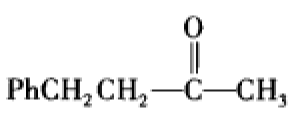
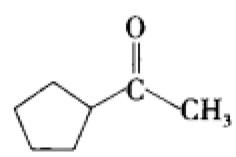
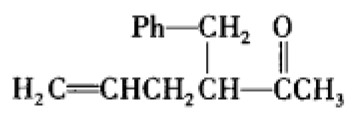


Hydrolysis proceeds with decarboxylation to give the disubstituted acetone product.



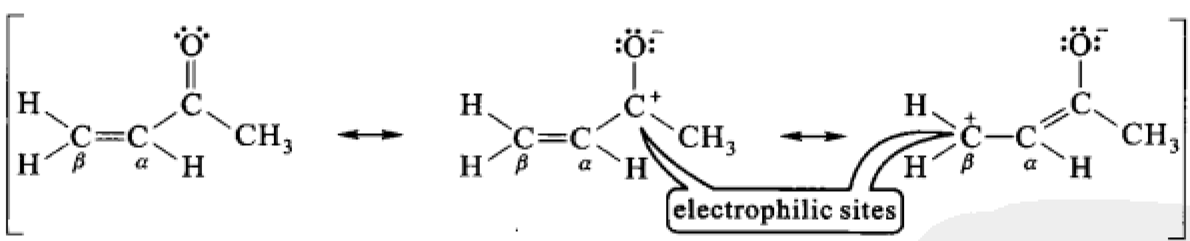
PROBLEM 23−20

Show how the following ketones might be synthesized by using the acetoacetic ester synthesis.

(a)  (b)  (c) 

23−17 Conjugate Additions: The Michael Reaction

α,β-Unsaturated carbonyl compounds have unusually electrophilic double bonds. The β carbon is electrophilic because it shares the partial positive charge of the carbonyl carbon through resonance.



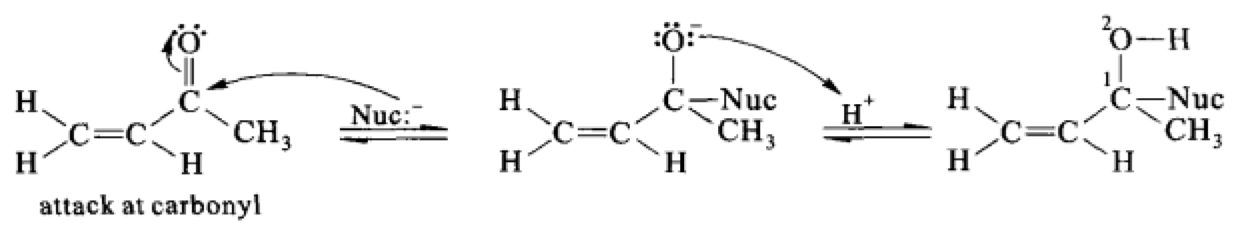
A nucleophile can attack an α,β-unsaturated carbonyl compound at either the carbonyl group or at the β position. When attack occurs at the carbonyl group, protonation of the oxygen leads to a **1,2-addition** product in which the nucleophile and the proton have added to adjacent atoms. When attack occurs at the β position, the oxygen atom is the fourth atom counting from the nucleophile, and the addition is called a **1,4-addition.** The net result of 1,4-addition is addition of the nucleophile and a hydrogen atom across a double bond that was conjugated with a carbonyl group. For this reason, 1,4-addition is often called **conjugate addition.**

MECHANISM 23−13 1,2-Addition and 1,4-Addition (Conjugate Addition)

1,2-addition

1,2-addition is the standard nucleophilic addition to a carbonyl group.

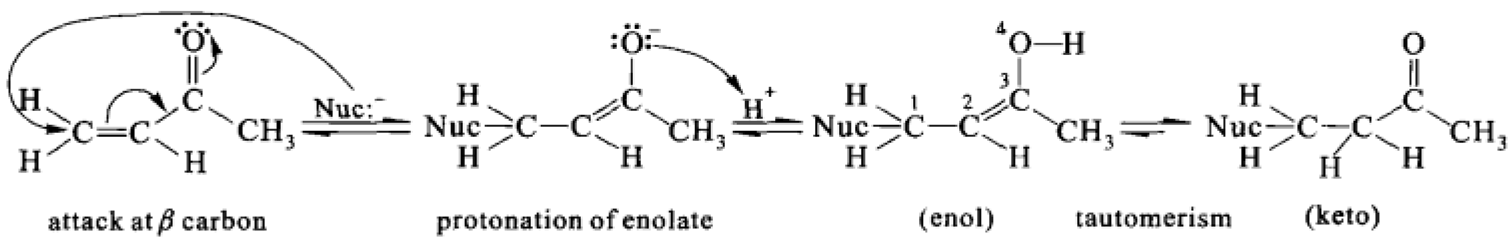
Step 1: Addition of the nucleophile to C=O. ***Step 2***: Protonation of the alkoxide.



1,4-addition (*conjugate addition or Michael addition*)

In a 1,4-addition, the nucleophile adds to the β carbon atom of an α,β-unsaturated system. Protonation may occur on oxygen to give an enol, or on carbon to give the keto form.

Step 1: Conjugate addition of the nucleophile. ***Step 2***: Protonation of the enolate.



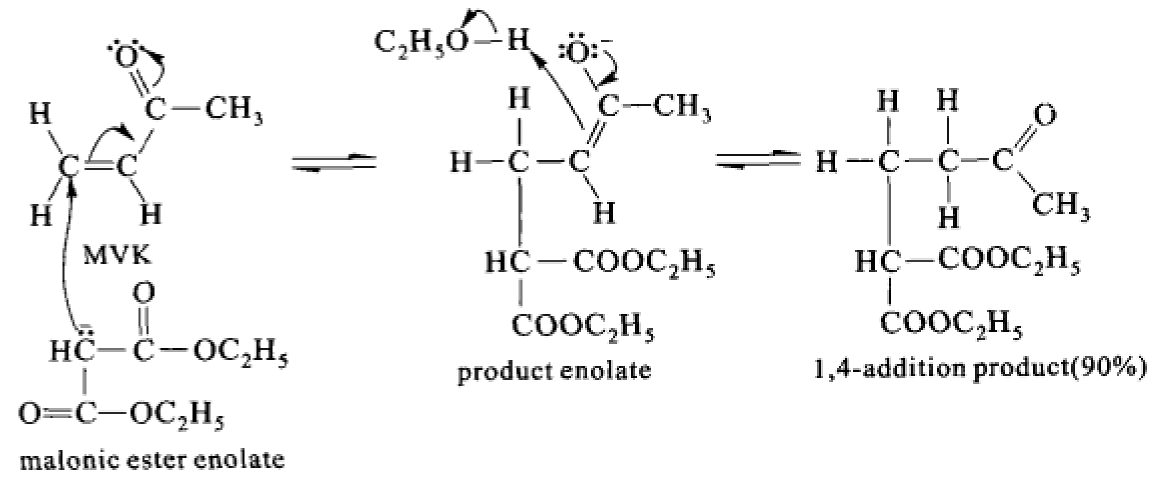
Conjugate addition of a carbanion to the double bond of an α,β-unsaturated carbonyl compound (or other electron-poor double bond) is called a **Michael addition.** The electrophile (the α,β-unsaturated carbonyl compound) accepts a pair of electrons; it is called the **Michael acceptor.** The attacking nucleophile donates a pair of electrons; it is called the **Michael donor.** A wide variety of compounds can serve as Michael donors and acceptors. Some of the common ones are shown in Table 23-2.

TABLE 23-2 Some Common Michael Donors and Michael Acceptors

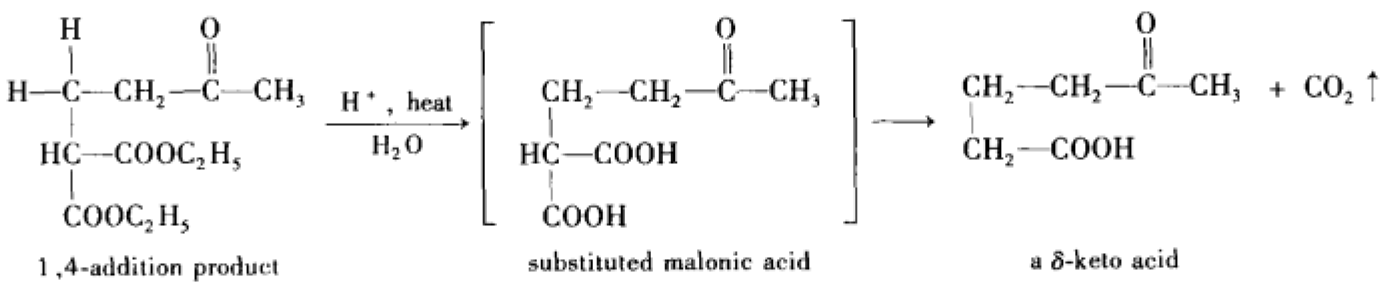
Michael Donors		Michael Acceptors	
R—C(=O)—C̈H—C(=O)—R′	β-diketone	H_2C=CH—C(=O)—H	conjugated aldehyde
R—C(=O)—C̈H—C(=O)—OR′	β-keto ester	H_2C=CH—C(=O)—R	conjugated ketone
R_2CuLi	dialkyl cuprate	H_2C=CH—C(=O)—OR	conjugated ester
>N̈—C=C<	enamine (烯胺)	H_2C=CH—C(=O)—NH_2	conjugated amide
R—C(=O)—C̈H—C≡N	β-keto nitrile	H_2C=CH—C≡N	conjugated nitrile
R—C(=O)—C̈H—NO_2	α-nitro ketone	H_2C=CH—NO_2	nitroethylene

Common donors are carbanions that are stabilized by two strong electron-withdrawing groups such as carbonyl groups, cyano groups, or intro groups. These nucleophiles are formed quantitatively by common bases, without extra base around to attack the Michael acceptor. Common acceptors contain a double bond conjugated with a carbonyl group, a cyano group, or a nitro group.

As an example, let's consider the addition of the malonic ester enolate to methyl vinyl ketone (MVK). The crucial step is the nucleophilic attack by the enolate at the carbon. The resulting enolate is strongly basic, and it is quickly protonated.

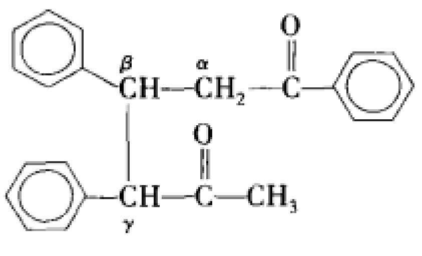


The product of this Michael addition may be treated like any other substituted malonic ester in the malonic ester synthesis. Hydrolysis and decarboxylation lead to a δ-keto acid. It is not easy to imagine other ways to synthesize this interesting keto acid.



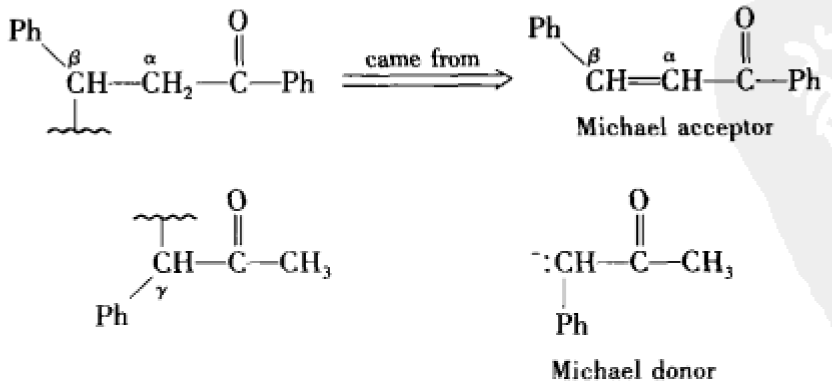
SOLVED PROBLEM 23-4

Show how the following diketone might be synthesized using a Michael addition.

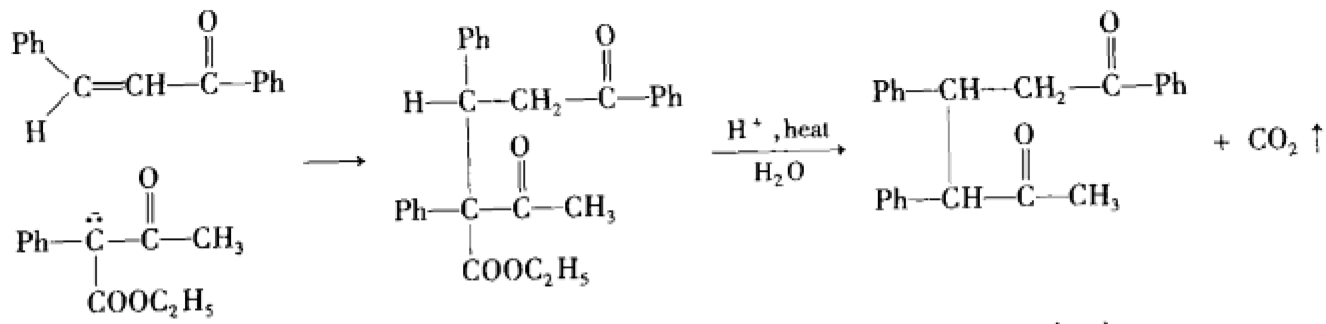


SOLUTION

A Michael addition would have formed a new bond at the β carbon of the acceptor. Therefore, we break this molecule apart at the β,γ bond.



The top fragment, where we broke the β bond, must have come from a conjugated ketone, and it must have been the Michael acceptor. The bottom fragment is a simple ketone. It is unlikely that this ketone was used without some sort of additional stabilizing group. We can add a temporary ester group to the ketone (making a substituted acetoacetic ester) and use the acetoacetic ester synthesis to give the correct product.

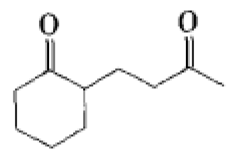


temporary ester group

target molecule

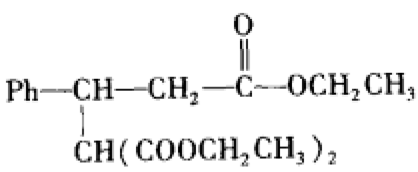
PROBLEM 23-21

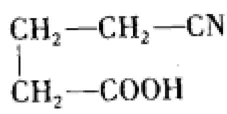
Show how cyclohexanone might be converted to the following δ-diketone. (*Hint*: Stork).

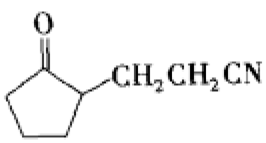


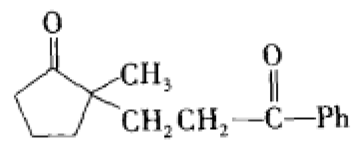
PROBLEM 23-22

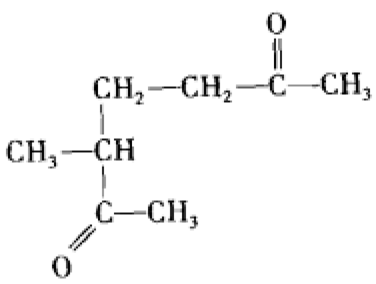
Show how the following products might be synthesized from suitable Michael donors and acceptors.

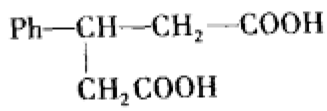
(a) 

(b) 

(c) 

(d) 

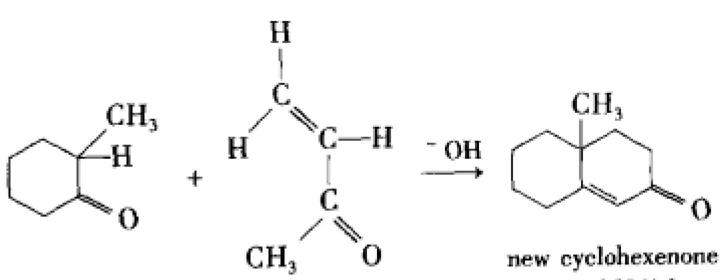
(e) 

(f) 

23-18 The Robinson Annulation

We have seen that Michael addition of a ketone enolate (or its enamine) to an α,β-unsaturated ketone gives a δ-diketone. If the conjugate addition takes place under strongly basic or acidic conditions, the δ-diketone undergoes a spontaneous intramolecular aldol condensation, usually with dehydration, to give a new six-membered ring: a conjugated cyclohexenone. This synthesis is called the **Robinson annulation** (ring-forming) reaction. Consider an example using a substituted cyclohexanone as the Michael donor and methyl vinyl ketone (MVK) as the Michael acceptor.

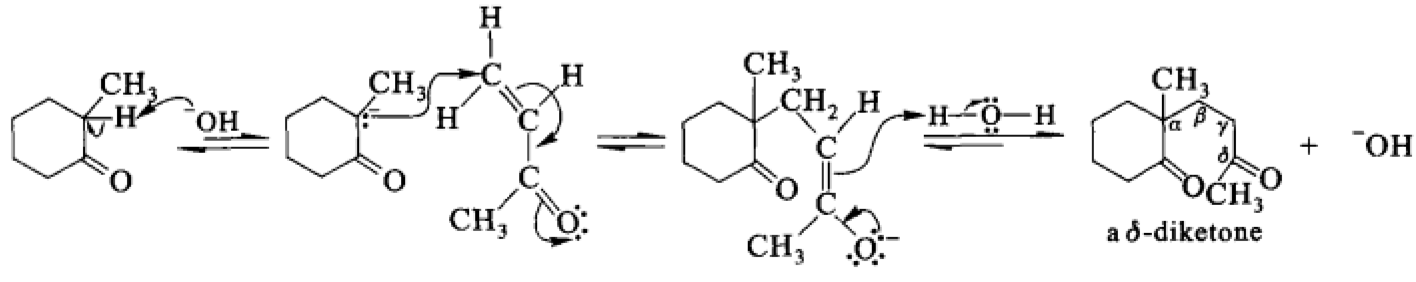
The Robinson annulation



new cyclohexenone
(65%)

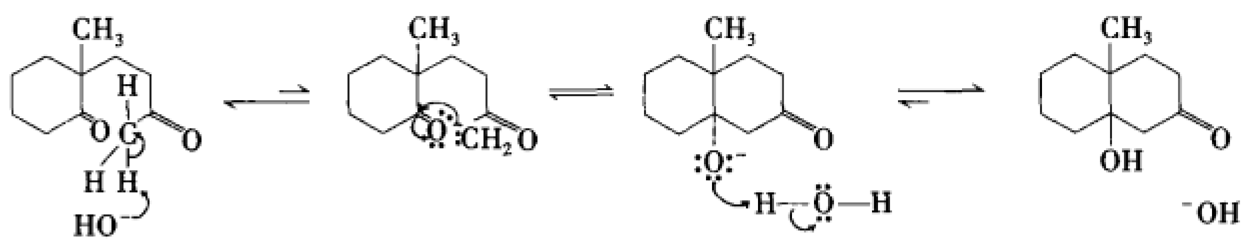
The mechanism begins with the Michael addition of the cyclohexanone enolate to MVK, forming a δ-diketone.

Step 1: Michael addition.

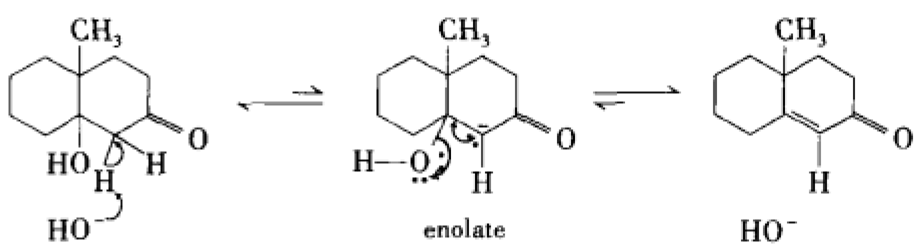


This δ-diketone might take part in several different aldol condensations, but it is ideally suited for a favorable one: formation of a six-membered ring. To form a six-membered ring, the enolate of the methyl ketone attacks the cyclohexanone carbonyl. The aldol product dehydrates to give a cyclohexenone.

Step 2: Cyclic aldol to form a 6-membered ring.



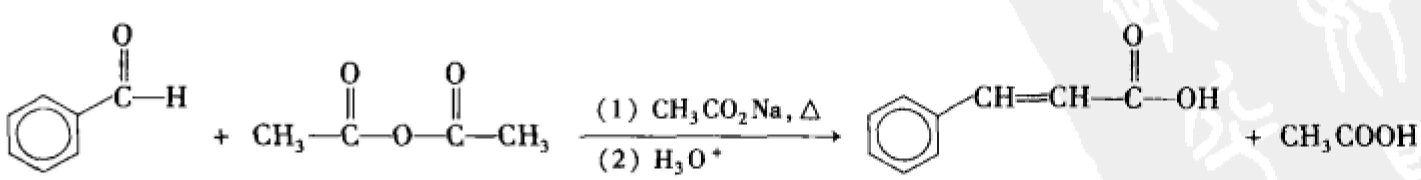
Step 3: Dehydration of the aldol product.



It is not difficult to predict the products of the Robinson annulation and to draw the mechanisms if you remember that the Michael addition is first, followed by an aldol condensation with dehydration to give a cyclohexenone.

PROBLEM 23-23

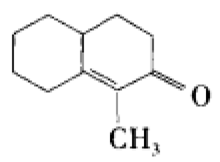
The base-catalyzed reaction of an aldehyde (having no α hydrogens) with an anhydride is called the *Perkin condensation*. Propose a mechanism for the following example of the Perkin condensation. (Sodium acetate serves as the base.)

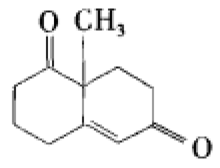


cinnamic acid (肉桂酸)

PROBLEM 23-24

Show how you would use Robinson annulations to synthesize the following compounds. Work backward, remembering that the cyclohexenone is the new ring and that the double bond of the cyclohexenone is formed by the aldol with dehydration. Take apart the double bond, then see what structures the Michael donor and acceptor must have.

(a) 

(b) 

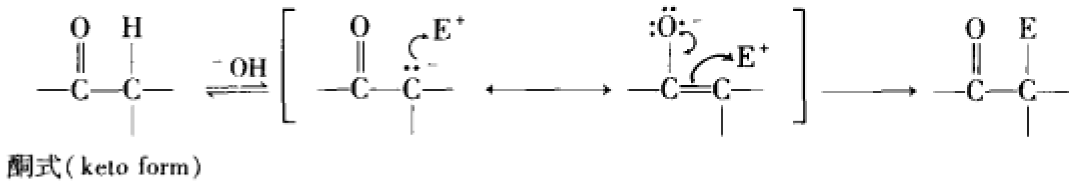
Summary in Chinese

本 章 概 要

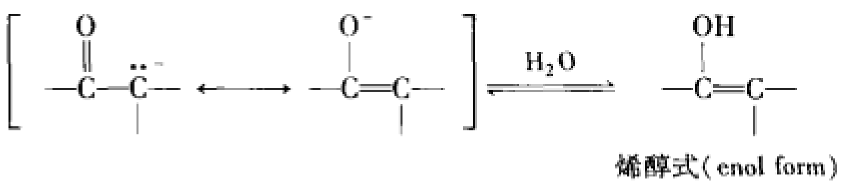
一、酮(醛)的 α-氢取代和缩合反应机理

酮(醛)分子中羰基原子的 α-氢可在碱性(某些情况下酸性也可以)条件下产生碳负离子,碳负离子是非常好的亲核试剂,可以发生亲核取代、亲核加成-消除(缩合反应)、亲核加成等反应。

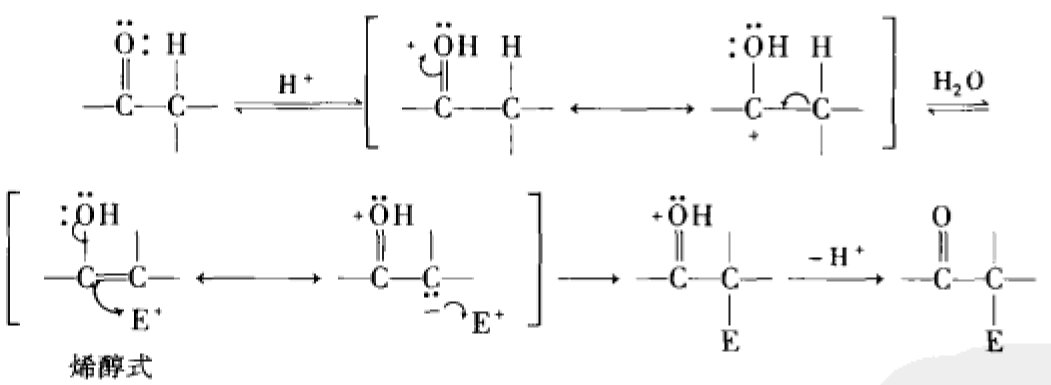
1. 碱性条件:



不与 E^+ 反应时,转化为烯醇式:



2. 酸性条件:



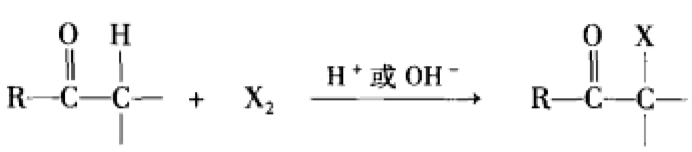
☆ 在碱性条件下,首先产生碳负离子,烯醇式的作用是稳定碳负离子;在酸性条件下,是先形成烯醇式,反应时,形成碳负离子。

☆ 除酮(醛)外,其他羰基化合物的 α-碳也能产生碳负离子,但需要比较强的碱性条件,如酯类化合物。

☆ 上面反应中的 E^+ 可以来自 X_2(α-卤代反应),RX(亲核取代),醛、酮(亲核加成反应即羟醛缩合反应),酯(亲核加成-消除反应如酯缩合反应)等亲电试剂。

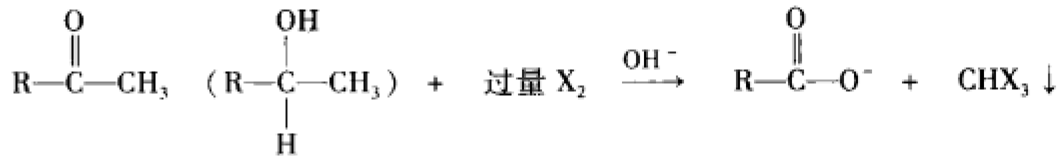
二、重要的 α-取代和缩合反应

1. 酮(醛)的 α-卤代:



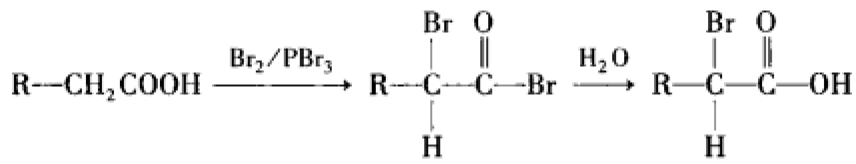
☆ 酸性条件下,单卤代产物;碱性条件下,可生成多卤代产物。

2. 卤仿反应:



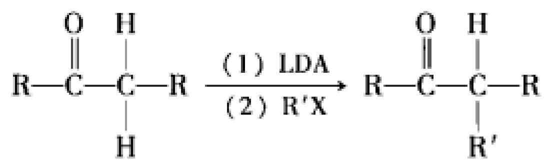
☆ 用于鉴别甲基酮(醇),可由酮制备少于一个碳原子的羧酸。

3. The Hell-Volhard-Zelinsky(HVZ)反应:



☆ 用于制备 α-卤代酸。

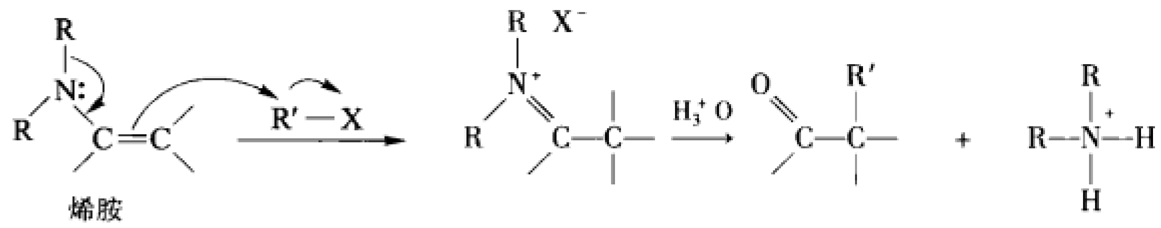
4. 烯醇锂的烷基化(alkylationof lithium enolates):



LDA = $(i\text{-Pr})_2$NLi,二异丙基胺锂(lithium diisopropylamide)

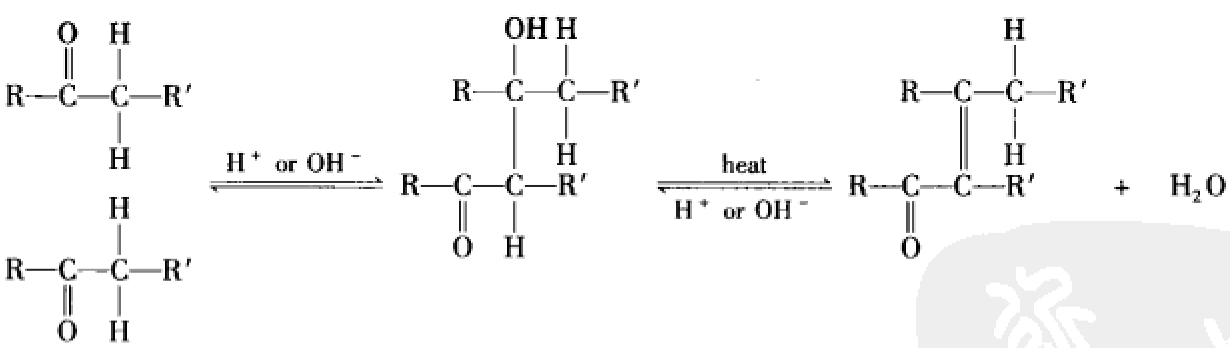
☆ LDA 具有强碱性、体积大而亲核性弱的特点,不与 RX 反应;R′X 是伯卤代烃或磺酸酯。

5. 烯胺烷基化(alkylation of enamines):



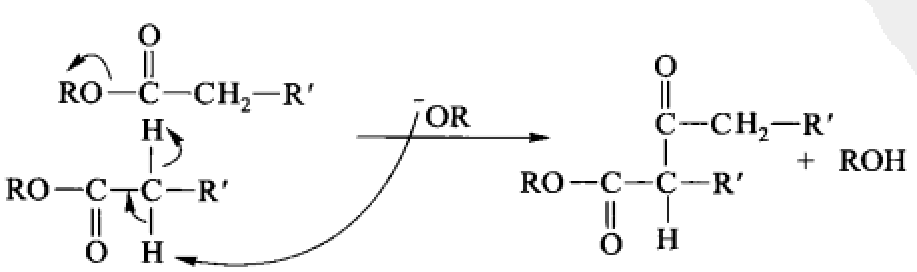
☆ 酮经过形成烯胺活化了酮的 α-碳,使酮的 α-碳原子负电性增加,更容易进行烷基化反应。

6. 羟醛缩合(aldol condensation and subsequent dehydration)



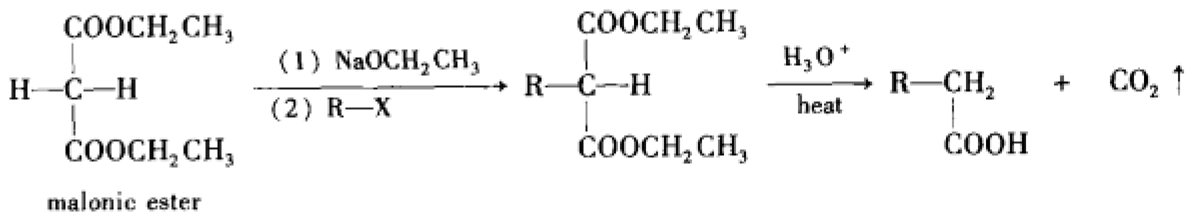
☆ 含有 α-H 的酮(醛)的性质;反应是可逆的;用于制备 β-羟基酮(醛)和 α,β-不饱和酮(醛);还可以发生交叉羟醛缩合反应和分子内羟醛缩合反应。

7. Claisen 酯缩合(Claisen ester condensation):



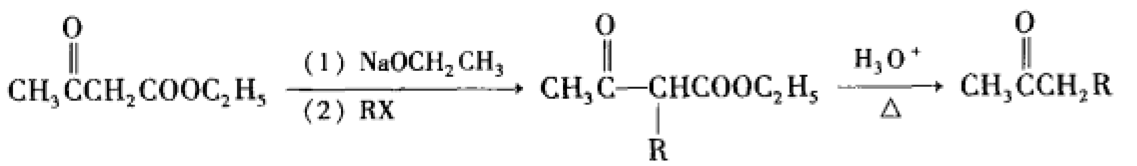
☆ 含有 $\alpha-H$ 的酯的性质，反应可逆；用于制备 $\beta-$酮酸酯，二元酸酯发生分子内酯缩合可以形成五元环或更大环的 $\beta-$酮酸酯，这种分子内酯缩合称为 Dieckmann 缩合；含 $\alpha-H$ 的酮（醛或酯）与无 $\alpha-H$ 的酯发生交叉的 Claisen 酯缩合在合成上可用于制备 $\beta-$二酮、$\beta-$酮醛及 $\beta-$酮酸酯化合物。

8. 丙二酸酯（malonic ester）合成酸：



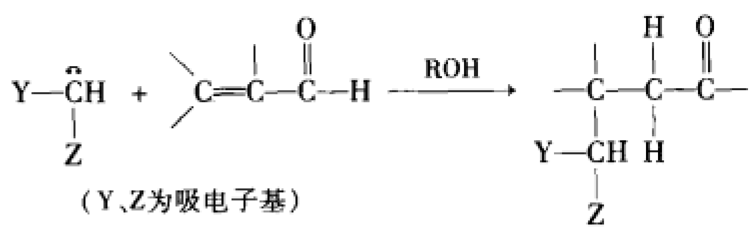
☆ 丙二酸酯含有活泼亚甲基，在碱性作用下产生碳负离子，然后与 RX 发生 S_N2 亲核取代反应，取代的丙二酸酯经过酯基水解、酸化、脱羧制备取代的乙酸；利用该反应与不同卤代烃的反应可制备一取代、二取代乙酸和环烷基羧酸。

9. 乙酰乙酸乙酯（acetoacetic ester）合成酮：



☆ 乙酰乙酸乙酯含有活泼的亚甲基，该反应的过程与丙二酸酯类似，利用该反应可制备一取代、二取代的丙酮。

10. Michael 加成（Michael addition）：



☆ Michael 加成反应用于合成多官能团化合物。

Essential Problem-Solving Skills in Chapter 23

This is a difficult chapter because condensations take on a wide variety of forms. You should try to *understand* the reactions and their mechanisms so you can generalize and predict related reactions. Work enough problems to get a feel for the standard reactions (aldol, Claisen, Michael) and to gain confidence in working out new variations of the standard mechanisms. Make sure you feel comfortable with condensations that form new rings.

1. Show how enols and enolate ions act as nucleophiles. Give mechanisms for acid-catalyzed and base-catalyzed keto-enol tautomerisms.

2. Give mechanisms for acid-catalyzed and base-promoted alpha halogenation of ketones and acid-catalyzed halogenation of acids (the HVZ reaction). Explain why multiple halogenation is common with basic catalysis, and give a mechanism for the haloform reaction.

3. Show how alkylation and acylation of enamines and lithium enolates are used synthetically. Give mechanisms for these reactions.

4. Predict the products of aldol and crossed aldol reactions before and after dehydration of the aldol products. Give mechanisms for the acid- and base-catalyzed reactions. (Aldols are reversible, so be sure you can write these mechanisms *backward* as well.) Show how aldols are used to make β-hydroxy carbonyl compounds and α,β-unsaturated carbonyl compounds.

5. Predict the products of Claisen and crossed Claisen condensations, and propose mechanisms. Show how a Claisen condensation constructs the carbon skeleton of a target compound.
6. Show how the malonic ester synthesis and the acetoacetic ester synthesis are used to make substituted acetic acids and substituted acetones. Give mechanisms for these reactions.
7. Predict the products of Michael additions, and show how to use these reactions in syntheses. Show the general mechanism of the Robinson annulation, and use it to form cyclohexenone ring systems.

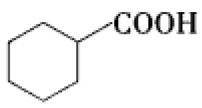
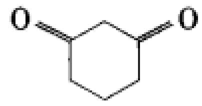
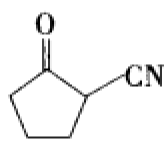
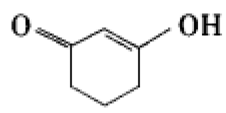
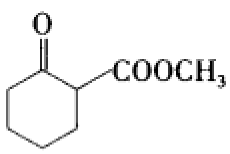
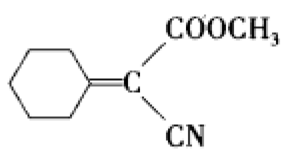
Study Problems

23-25 Define each term and give an example.

(a) keto-enol tautomerism (b) enolizable hydrogen (c) enolate ion
(d) haloform reaction (e) HVZ reaction (f) enamine
(g) Stork reaction (h) alpha substitution (i) aldol condensation
(j) crossed aldol condensation (k) Claisen condensation (l) crossed Claisen condensation
(m) Dieckmann condensation (n) condensation (o) malonic ester synthesis
(p) acetoacetic ester synthesis (q) Michael addition (r) Robinson annulation

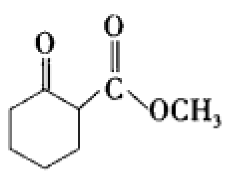
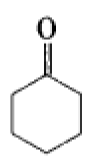
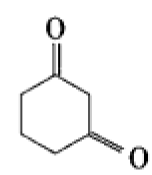
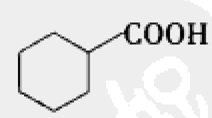
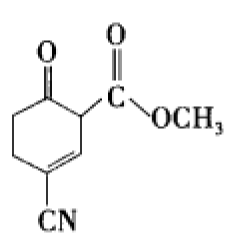
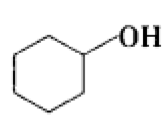
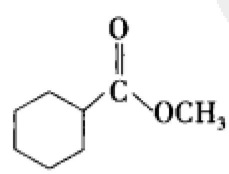
23-26 For each molecule shown below.

1. indicate the most acidic hydrogens.
2. draw the important resonance contributors of the anion that results from removal of the most acidic hydrogen.

(a) 
(b) 
(c) 
(d) 
(e) 
(f) 

(g) $CH_3—CH{=}CH—\overset{O}{\overset{\|}{C}}—H$
(h) $CH_2{=}CH—CH_2—\overset{O}{\overset{\|}{C}}—H$

23-27 1. Rank the following compounds in order of increasing acidity.
2. Indicate which compounds would be more than 99% deprotonated by a solution of sodium ethoxide in ethanol.

(a) 
(b) 
(c) 
(d) 
(e) 
(f) 
(g) 

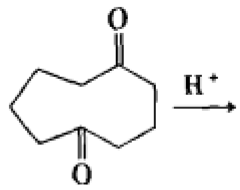
23-28 Pentane-2,4-dione (acetylacetone) exists as a tautomeric mixture of 8% keto and 92% enol forms. Draw the stable enol tautomer, and explain its unusual stability.

$$CH_3—\overset{O}{\overset{\|}{C}}—CH_2—\overset{O}{\overset{\|}{C}}—CH_3$$

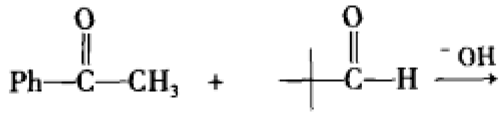
acetylacetone

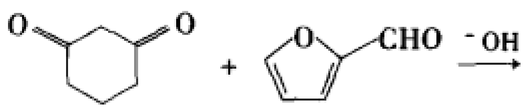
23–29 Predict the products of the following aldol condensations. Show the products both before and after dehydration.

(a) $(CH_3)_2CH-CH_2-\overset{O}{\overset{\|}{C}}-H \xrightarrow{^-OH}$

(b) 

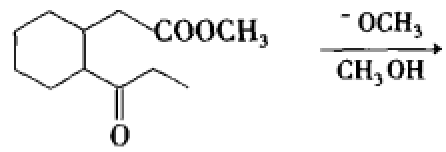
(c) $2Ph-CHO + CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{^-OH}$

(d) 

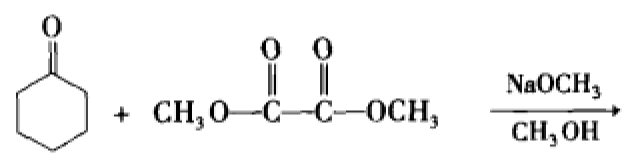
(e) 

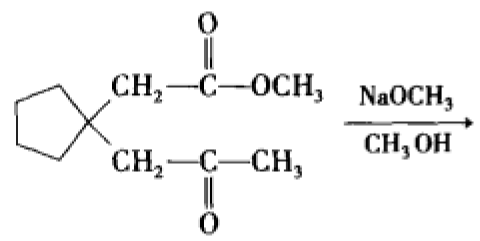
23–30 Predict the products of the following Claisen condensations.

(a) $(CH_3)_2CH-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3 \xrightarrow[CH_3OH]{^-OCH_3}$

(b) 

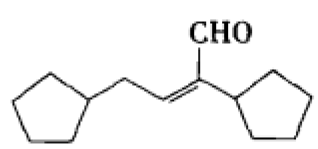
(c) $CH_3CH_2-\overset{O}{\overset{\|}{C}}-CH_2CH_2CH_2CH_2-\overset{O}{\overset{\|}{C}}-OCH_3 \xrightarrow[CH_3OH]{^-OCH_3}$ (Dieckmann)

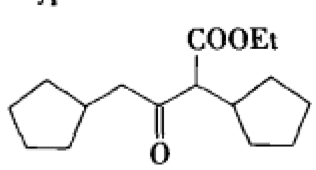
(d) 

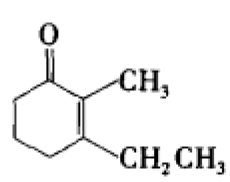
(e) 

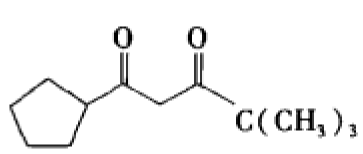
23–31 Propose mechanisms for the reactions shown in Problems 23–29 parts (a) and (b) and 23–30 parts (a) and (b).

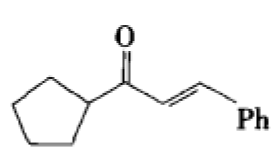
23–32 Show how you would use an aldol, Claisen, or other type of condensation to make each compound.

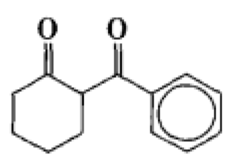
(a) 

(b) 

(c) 

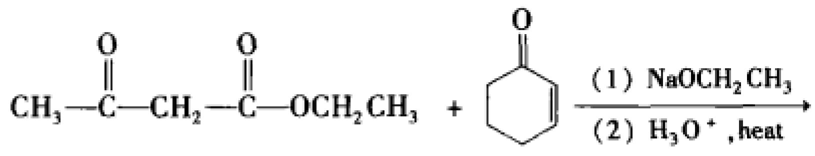
(d) 

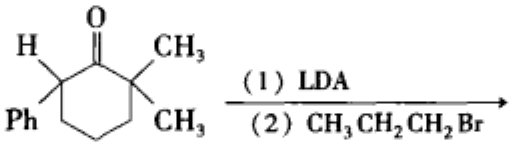
(e) 

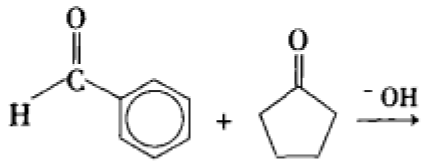
(f) 

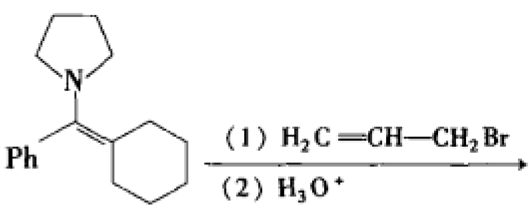
23–33 Predict the products of the following reactions.

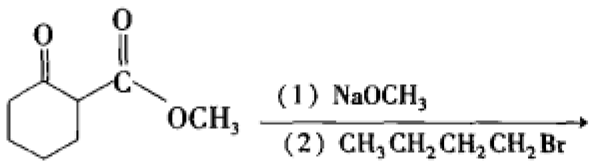
(a) $CH_3CH_2-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3 \xrightarrow[(2)\ CH_3I]{(1)\ NaOCH_3}$ (3) H_3O^+, heat

(b) 

(c) 

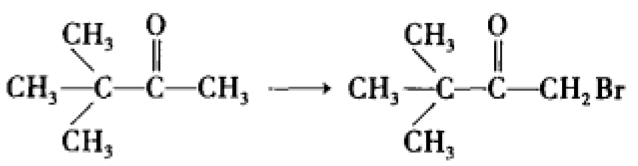
(d) 

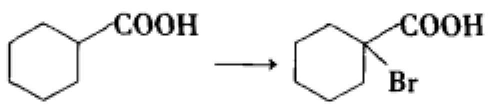
(e) 

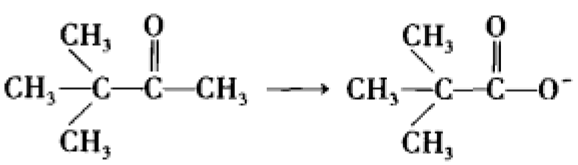
(f) 

(g) product from part (f) $\xrightarrow[\text{heat}]{H_3O^+}$ (decarboxylation)

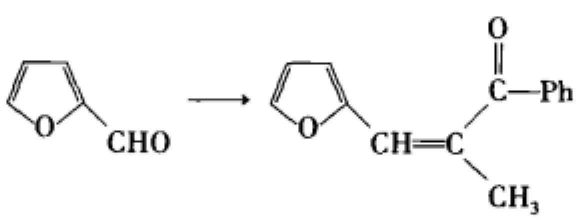
23–34 Show how you would accomplish the following conversions in good yields. You may use any necessary reagents.

(a) 

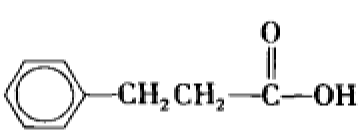
(b) 

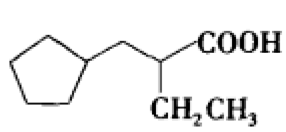
(c) 

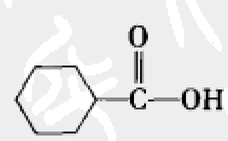
(d)

(e)  (*Hint*: aldol)

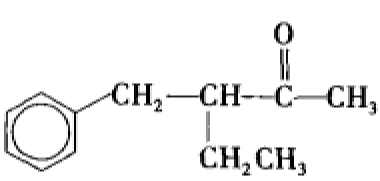
23–35 Show how you would use the malonic ester synthesis to make the following compounds.

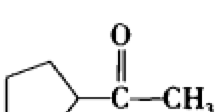
(a) 

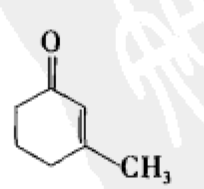
(b) 

(c) 

23–36 Show how you would use the acetoacetic ester synthesis to make the following compounds.

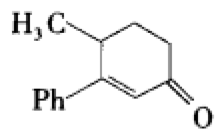
(a) 

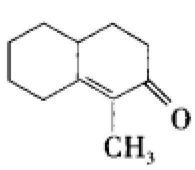
(b) 

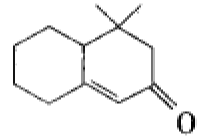
(c) 

(*Hint*: Consider using 2,6-heptanedione as an intermediate.)

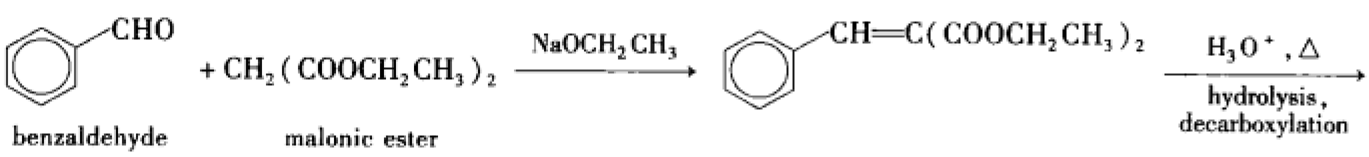
23−37 Show how you would use the Robinson annulation to synthesize the following compounds.

(a) 

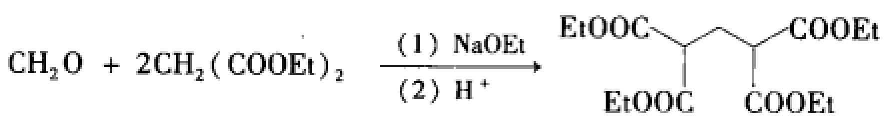
(b) 

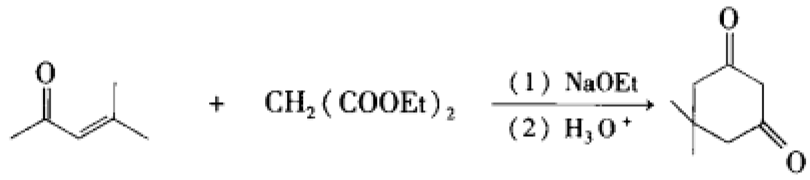
(c) 

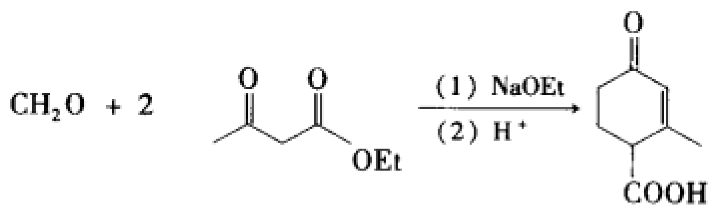
23−38 Propose a mechanism for the following reaction. Show the structure of the compound that results from hydrolysis and decarboxylation of the product.



***23−39** Show reaction sequences (not detailed mechanisms) that explain these transformations:

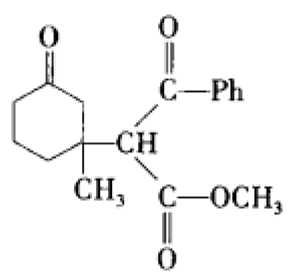
(a) 

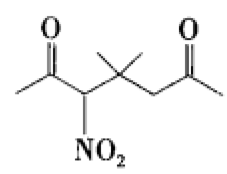
(b) 

(c) 

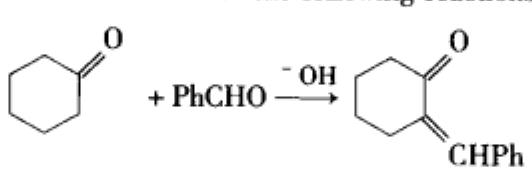
***23−40** The following compounds can be synthesized by aldol condensations, followed by further reactions. (In each case, work backward from the target molecule to an aldol product, and show what compounds are needed for the condensation.)

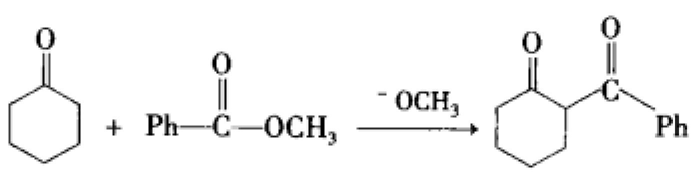
(a) Ph—CH$_2$—CH$_2$—CH(OH)—Ph

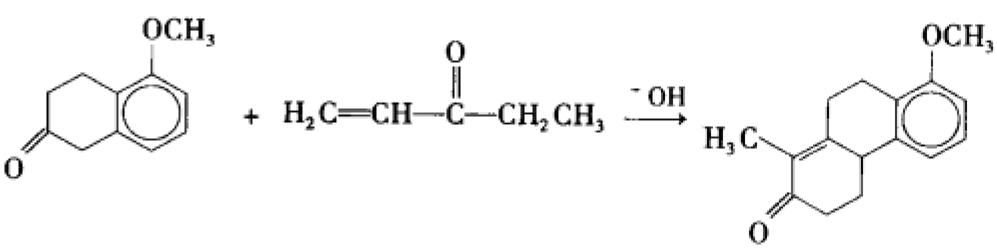
(b) 

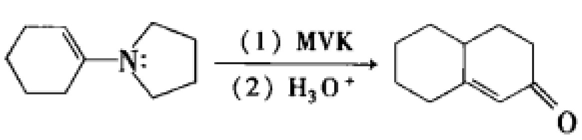
(c) 

23−41 Propose mechanisms for the following reactions.

(a) 

(b) 

(c) 

(d) 

23-42 Write equations showing the expected products of the following enamine alkylation and acylation reactions. Then give the final products expected after hydrolysis of the iminium salts.

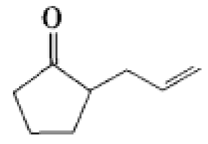
(**a**) pyrrolidine enamine of 3-pentanone + allyl chloride

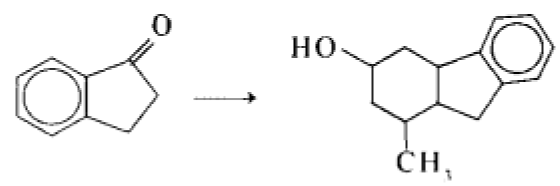
(**b**) pyrrolidine enamine of acetophenone + butanoyl chloride

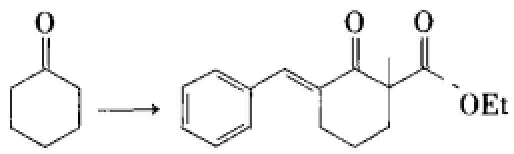
(**c**) piperidine enamine of cyclopentanone + methyl iodide

(**d**) piperidine enamine of cyclopentanone + methyl vinyl ketone

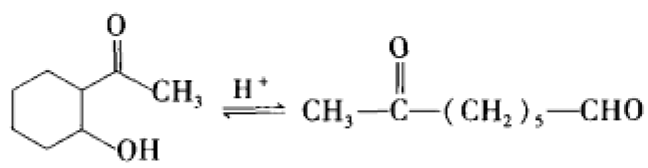
***23-43** Show how you would accomplish the following multistep conversions. You may use any additional reagents you need.

(**a**) dimethyl adipate and allyl bromide ⟶ 

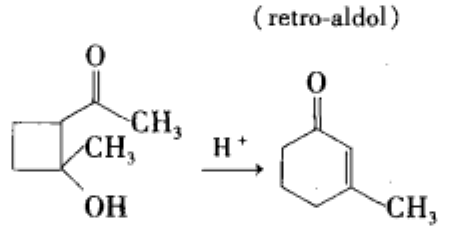
(**b**) 

(**c**) 

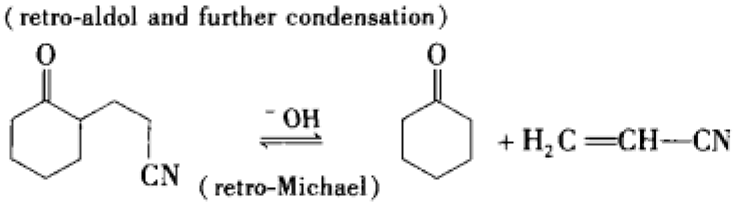
***23-44** Many of the condensations we have studied are reversible. The reverse reactions are often given the prefix *retro-*, the Latin word meaning "backward." Propose mechanisms to account for the following reactions.

(**a**) 

(retro-aldol)

(**b**) 

(retro-aldol and further condensation)

(**c**) 

Chapter 24

Carbohydrates and Nucleic Acids

24–1 Introduction

Carbohydrates are the most abundant organic compounds in nature. Nearly all plants and animals synthesize and metabolize carbohydrates, using them to store energy and deliver it to their cells. Plants synthesize carbohydrates through *photo-synthesis*, a complex series of reactions that use sunlight as the energy source to convert carbon dioxide and water into glucose and oxygen. Many molecules of glucose can be linked together to form either *starch* for energy storage or *cellulose* to support the plant.

$$6\ CO_2 + 6\ H_2O \xrightarrow{\text{light}} 6\ O_2 + \underset{\substack{\text{glucose} \\ \text{(葡萄糖)}}}{C_6H_{12}O_6} \longrightarrow \underset{\text{(淀粉)，(纤维素)}}{\text{starch, cellulose}} + H_2O$$

Most living organisms oxidize glucose to carbon dioxide and water to provide the energy needed by their cells. Plants can retrieve the glucose units from starch when needed. In effect, starch is a plant's storage unit for solar energy for later use. Animals can also store glucose energy by linking many molecules together to form *glycogen*, another form of starch. *Cellulose* makes up the cell walls of plants and forms their structural framework. Cellulose is the major component of *wood*, a strong yet supple material that supports the great weight of the oak, yet allows the willow to bend with the wind.

Almost every aspect of human life involves carbohydrates in one form or another. Like other animals, we use the energy content of carbohydrates in our food to produce and store energy in our cells. Clothing is made from cotton and linen, two forms of cellulose. Other fabrics are made by manipulating cellulose to convert it to the semisynthetic fibers *rayon* and *cellulose acetate*. In the form of wood, we use cellulose to construct our houses and as a fuel to heat them. Even this page is made from cellulose fibers.

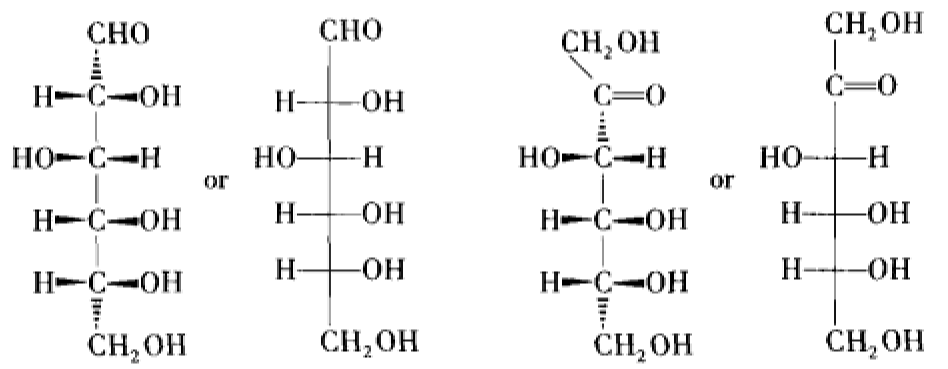
Carbohydrate chemistry is one of the most interesting areas of organic chemistry. Many chemists are employed by companies that use carbohydrates to make foods, building materials, and other consumer products. All biologists need to understand carbohydrates, which play pivotal roles throughout the plant and animal kingdoms. At first glance, the structures and reactions of carbohydrates may seem complicated. We will learn how these structures and reactions are consistent and predictable, however, and we can study carbohydrates as easily as we study the simplest organic compounds.

24-2 Classification of Carbohydrates

The term **carbohydrate** arose because most **sugars** have molecular formulas $C_n(H_2O)_m$, suggesting that carbon atoms are combined in some way with water. In fact, the empirical formula of most simple sugars is $C(H_2O)$. Chemists named these compounds "hydrates of carbon" or "carbohydrates" because of these molecular formulas. Our modern definition of carbohydrates includes polyhydroxyaldehydes, polyhydroxyketones, and compounds that are easily hydrolyzed to them.

Monosaccharides, or *simple sugars*, are carbohydrates that cannot be hydrolyzed to simpler compounds. Figure 24-1 shows Fischer projections of the monosaccharides *glucose* and *fructose*. Glucose is a polyhydroxyaldehyde, and fructose is a polyhydroxyketone. Polyhydroxyaldehydes are called **aldoses** (*ald-* is for *ald*ehyde and- *ose* is the suffix for a sugar), and polyhydroxyketones are called **ketoses** (*ket-* for *ket*one, and- *ose* for sugar).

We have used Fischer projections to draw the structures of glucose and fructose because Fischer projections conveniently show the stereochemistry at all the asymmetric carbon atoms. The Fischer projection was originally developed by Emil Fischer, a carbohydrate chemist who received the Nobel Prize for his proof of the structure of glucose. Fischer developed this shorthand notation for drawing and comparing sugar structures quickly and easily. We will use Fischer projections extensively in our work with carbohydrates, so you may want to review them and make models of the structures in Figure 24-1 to review the stereochemistry implied by these structures. In aldoses, the aldehyde carbon is the most highly oxidized (and numbered 1 in the IUPAC name), so it is always at the top of the Fischer projection. In ketoses, the carbonyl group is usually the second carbon from the top.



glucose (葡萄糖) fructose (果糖)

Figure 24-1 Fischer projections of sugars.

PROBLEM 24-1

Draw the mirror images of glucose and fructose. Are glucose and fructose chiral? Do you expect them to be optically active?

A **disaccharide** is a sugar that can be hydrolyzed to two monosaccharides. For example, sucrose ("table sugar") is a disaccharide that can be hydrolyzed to one molecule of glucose and one molecule of fructose.

$$1 \text{ sucrose} \xrightarrow[\text{heat}]{H_3O^+} 1 \text{ glucose} + 1 \text{ fructose}$$

(蔗糖)

Both monosaccharides and disaccharides are highly soluble in water, and most have the characteristic sweet taste

we associate with sugars.

Polysaccharides are carbohydrates that can be hydrolyzed to many monosaccharide units. Polysaccharides are naturally occurring polymers (*biopolymers*) of carbohydrates. They include starch and cellulose, both biopolymers of glucose. **Starch** is a polysaccharide whose carbohydrate units are easily added to store energy or removed to provide energy to cells. The polysaccharide **cellulose** is a major structural component of plants. Hydrolysis of either starch or cellulose gives many molecules of glucose.

$$\text{starch (淀粉)} \xrightarrow[\text{heat}]{H_3O^+} \text{over 1 000 glucose molecules}$$

$$\text{cellulose (纤维素)} \xrightarrow[\text{heat}]{H_3O^+} \text{over 1 000 glucose molecules}$$

To understand the chemistry of these more complex carbohydrates, we must first learn the principles of carbohydrate structure and reactions, using the simplest monosaccharides as examples. Then we will apply these principles to more complex disaccharides and polysaccharides. The chemistry of carbohydrates applies the chemistry of alcohols, aldehydes, and ketones to these polyfunctional compounds. In general, the chemistry of biomolecules can be predicted by applying the chemistry of simple organic molecules with similar functional groups.

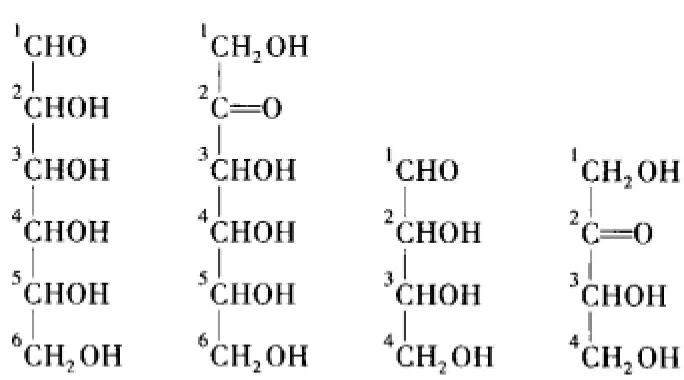
24-3 Monosaccharides

24-3A Classification of Monosaccharides

Most sugars have their own specific common names, such as glucose, fructose, galactose, and mannose. These names are not systematic, although there are simple ways to remember the common structures. We simplify the study of monosaccharides by grouping similar structures together. Three criteria guide the classification of monosaccharides:

1. Whether the sugar contains a ketone or an aldehyde group
2. The number of carbon atoms in the carbon chain
3. The stereochemical configuration of the asymmetric carbon atom farthest from the carbonyl group

As we have seen, sugars with aldehyde groups are called **aldoses**, and those with ketone groups are called **ketoses**. The number of carbon atoms in the sugar generally ranges from three to seven, designated by the terms *triose* (three carbons), *tetrose* (four carbons), *pentose* (five carbons), *hexose* (six carbons), and *heptose* (seven carbons). Terms describing sugars often reflect these first two criteria. For example, glucose has an aldehyde and contains six carbon atoms, so it is an aldohexose. Fructose also contains six carbon atoms, but it is a ketone, so it is called a ketohexose. Most ketoses have the ketone on C2, the second carbon atom of the chain. The most common naturally occurring sugars are aldohexoses and aldopentoses.



an aldohexose (己醛糖)　a ketohexose (己酮糖)　an aldotetrose (丁醛糖)　a ketotetrose (丁酮糖)

PROBLEM 24-2

(a) How many asymmetric carbon atoms are there in an aldotetrose? Draw all the aldotetrose stereoisomers.

(b) How many asymmetric carbons are there in a ketotetrose? Draw all the ketotetrose stereoisomers.

(c) How many asymmetric carbons and stereoisomers are there for an aldohexose? For a ketohexose?

PROBLEM 24-3

(a) There is only one ketotriose, called *dihydroxyacetone*. Draw its structure.

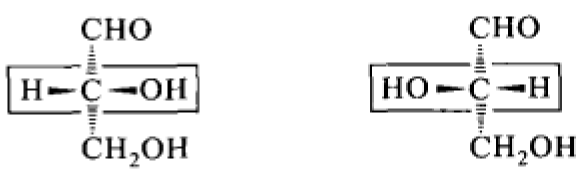
(b) There is only one aldotriose, called *glyceraldehyde*. Draw the two enantiomers of glyceraldehyde.

24-3B The D and L Configurations of Sugars

Around 1880-1900, carbohydrate chemists made great strides in determining the structures of natural and synthetic sugars. They found ways to build larger sugars out of smaller ones, adding a carbon atom to convert a tetrose to a pentose and a pentose to a hexose. The opposite conversion, removing one carbon atom at a time (called a *degradation*), was also developed. A degradation could convert a hexose to a pentose, a pentose to a tetrose, and a tetrose to a triose. There is only one aldotriose, glyceraldehyde.

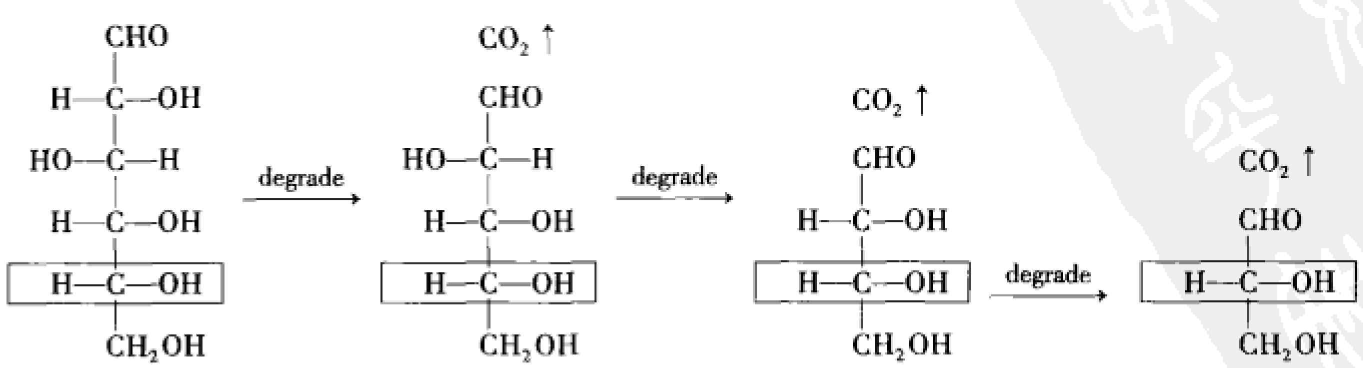
These chemists noticed they could start with any of the naturally occurring sugars, and degradation to glyceraldehyde always gave the dextrorotatory (+) enantiomer of glyceraldehyde. Some synthetic sugars, on the other hand, degraded to the levorotatory (−) enantiomer of glyceraldehyde. Carbohydrate chemists started using the *Fischer-Rosanoff convention*, which uses a D to designate the sugars that degrade to (+) glyceraldehyde and an L for those that degrade to (−) glyceraldehyde. Although these chemists did not know the absolute configurations of any of these sugars, the D and L relative configurations were useful to distinguish the naturally occurring D sugars from their unnatural L enantiomers.

We now know the absolute configurations of (+) and (−) glyceraldehyde. These structures serve as the configurational standards for all monosaccharides.



(+)-glyceraldehyde (甘油醛) D series of sugars　　(−)-glyceraldehyde L series of sugars

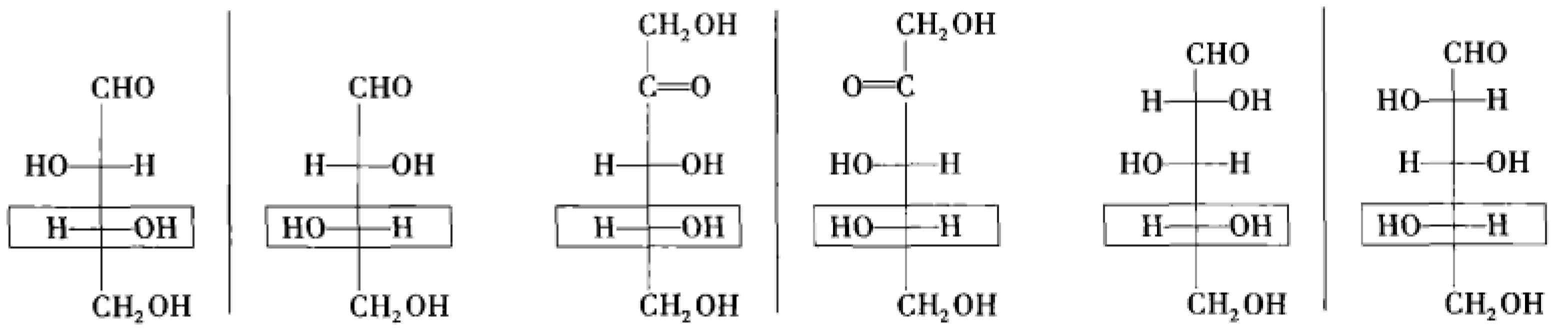
Figure 24-2 shows that degradation removes the aldehyde carbon atom, and it is the *bottom asymmetric carbon* in the Fischer projection (the asymmetric carbon farthest removed from the carbonyl group) that determines which enantiomer of glyceraldehyde is formed by successive degradations.



D-(+)-glucose D−(+)−葡萄糖　　D-(−)-arabinose D−(−)−阿拉伯糖　　D-(−)-erythrose D−(−)−赤藓糖　　D-(+)-glyceraldehyde D−(+)−甘油醛

Figure 24-2 Degradation to glyceraldehyde.

We now know that the (+) enantiomer of glyceraldehyde has its OH group on the right in the Fischer projection, as shown in Figure 24−2. Therefore, sugars of the **D series** have the OH group of the bottom asymmetric carbon on the right in the Fischer projection. Sugars of the **L series**, in contrast, have the OH group of the bottom asymmetric carbon on the left. In the following examples, notice that the D or L configuration is determined by the bottom asymmetric carbon, and the enantiomer of a D sugar is always an L sugar.



D-threose (D−苏阿糖) | L-threose (L−苏阿糖) | D-ribulose (D−核糖) | L-ribulose (L−核糖) | D-xylose (D−木糖) | L-xylose (D−木糖)

As mentioned earlier, most naturally occurring sugars have the D configuration, and most members of the D family of aldoses (up through six carbon atoms) are found in nature. Figure 24−3 shows the D family of aldoses. Notice that the D or L configuration does not tell us which way a sugar rotates the plane of polarized light. This must be determined by experiment. Some D sugars have (+) rotations, and others have (−) rotations.

At the time the D and L system of relative configurations was introduced, chemists could not determine the absolute configurations of chiral compounds. They decided to draw the D series with the glyceraldehyde OH group on the right, and the L series with it on the left. This guess later proved to be correct, so it was not necessary to revise all the old structures.

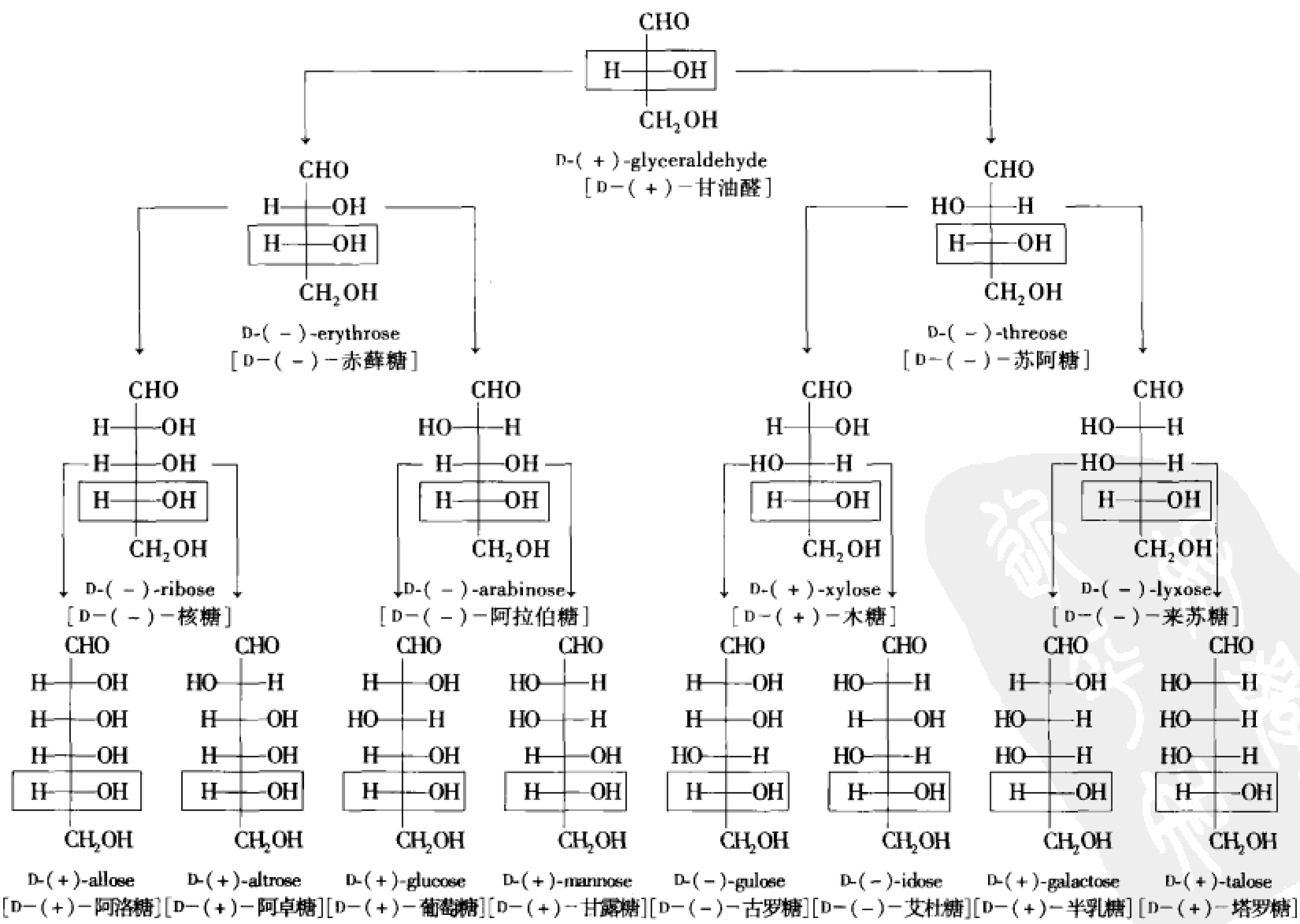


Figure 24−3 The D family of aldoses. All these sugars occur naturally except for threose, lyxose, allose, and gulose.

PROBLEM 24-4

Draw and name the enantiomers of the sugars shown in Figure 24-2. Give the relative configuration (D or L) and the sign of the rotation in each case.

PROBLEM 24-5

Which configuration (*R* or *S*) does the bottom asymmetric carbon have for the D series of sugars? Which configuration for the L series?

24-4 Erythro and Threo Diastereomers

Erythrose is the aldotetrose with the OH groups of its two asymmetric carbons situated on the same side of the Fischer projection, and *threose* is the diastereomer with the OH groups on opposite sites of the Fischer projection. These names have evolved into a shorthand way of naming diastereomers with two adjacent asymmetric carbon atoms. A diastereomer is called **erythro** if its Fischer projection shows similar groups on the same side of the molecule. It is called **threo** if similar groups are on opposite sides of the Fischer projection.

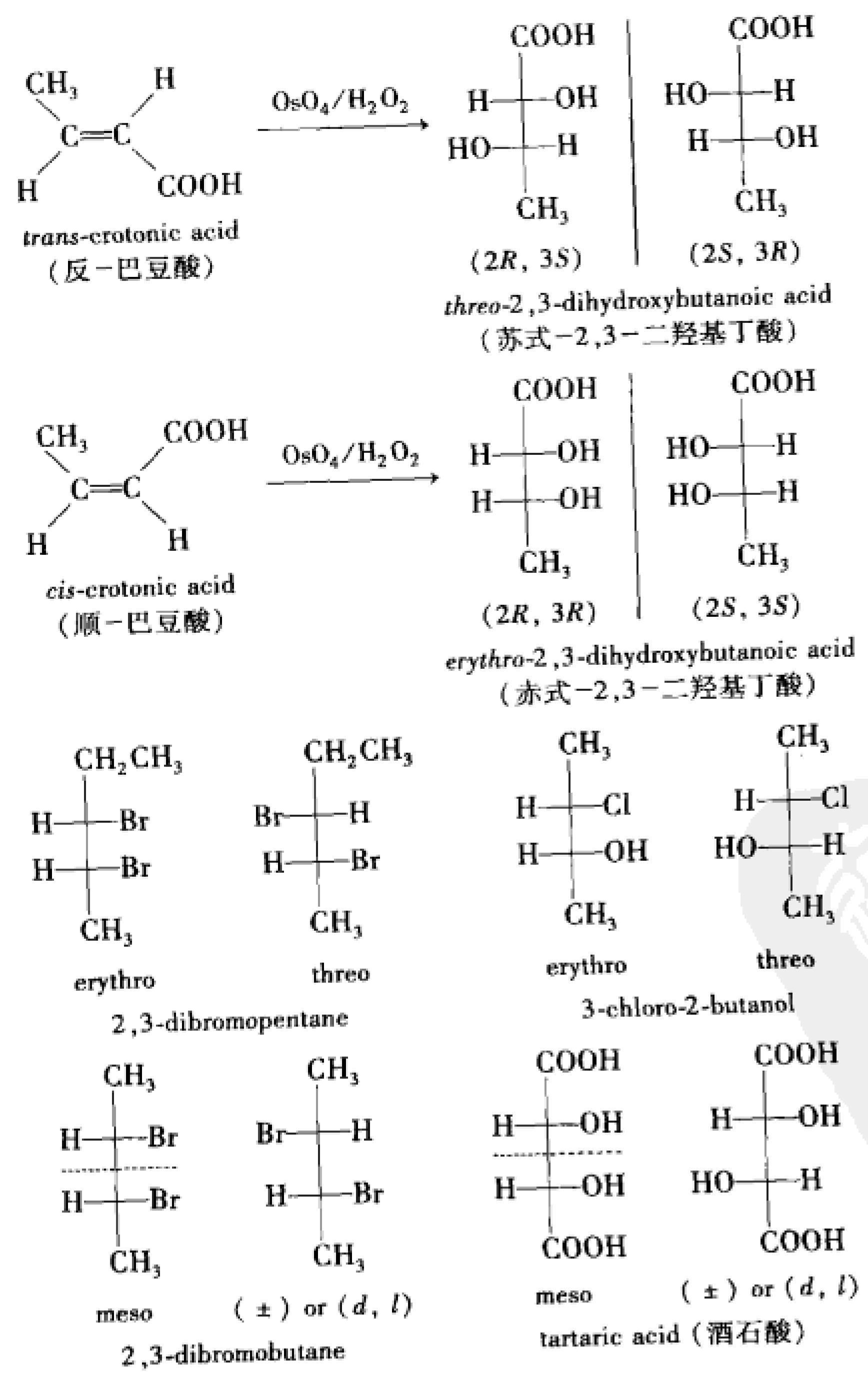


Figure 24-4 *Erythro* and *threo* nomenclature.

For example, syn hydroxylation of *trans*-crotonic acid gives two enantiomers of the threo diastereomer of 2,3-dihydroxybutanoic acid. The same reaction with *cis*-crotonic acid gives the erythro diastereomer of the product.

The terms *erythro* and *threo* are generally used only with molecules that do not have symmetric ends. In symmetric molecules such as 2,3-dibromobutane and tartaric acid, the terms *meso* and (d, l) are preferred because these terms indicate the diastereomer and tell whether or not it has an enantiomer. Figure 24–4 shows the proper use of the terms *erythro* and *threo* for dissymmetric molecules, as well as the terms *meso* and (d, l) for symmetric molecules.

24–5 Epimers

Many common sugars are closely related, differing only by the stereochemistry at a single carbon atom. For example, glucose and mannose differ only at C2, the first asymmetric carbon atom. Sugars that differ only by the stereochemistry at a single carbon are called **epimers**, and the carbon atom where they differ is generally stated. If the number of a carbon atom is not specified, it is assumed to be C2. Therefore, glucose and mannose are "C2 epimers" or simply "epimers." The C4 epimer of glucose is galactose, and the C2 epimer of erythrose is threose. These relationships are shown in Figure 24–5.

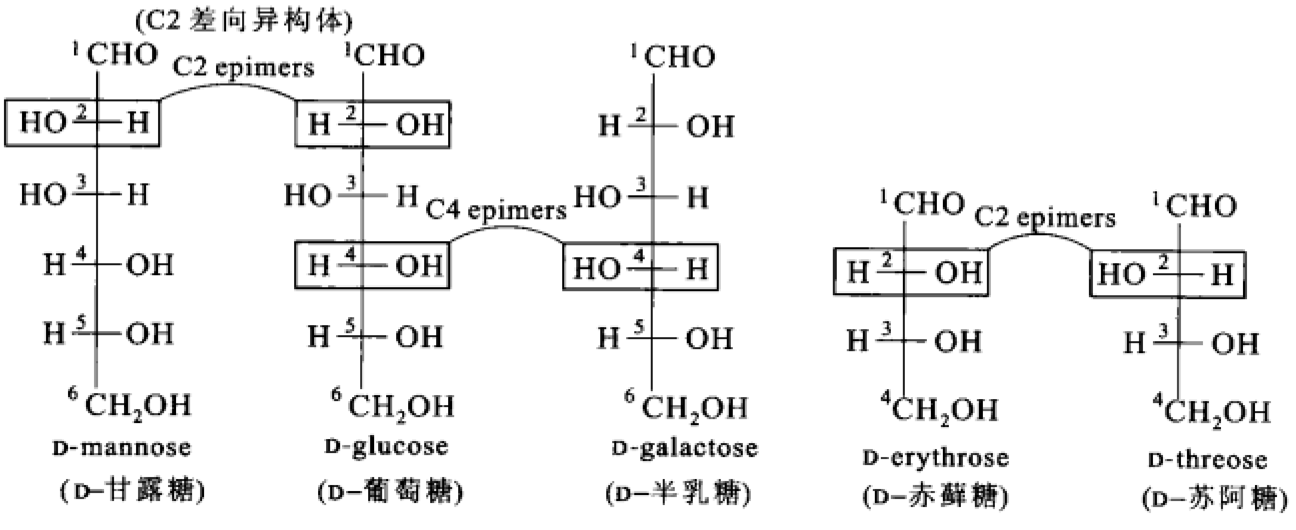


Figure 24–5 Epimers. Epimers are sugars that differ only by the stereochemistry at a single carbon atom. If the number of the carbon atom is not specified, it is assumed to be C2.

24–6 Cyclic Structures of Monosaccharides

Cyclic Hemiacetals In Chapter 19, we saw that an aldehyde reacts with one molecule of an alcohol to give a hemiacetal, and with a second molecule of the alcohol to give an acetal. The hemiacetal is not as stable as the acetal, and most hemiacetals decompose spontaneously to the aldehyde and the alcohol. Therefore, hemiacetals are rarely isolated.

If the aldehyde group and the hydroxyl group are part of the same molecule, a cyclic hemiacetal results. Cyclic hemiacetals are particularly stable if they result in five- or six- membered rings. In fact, five-and six-membered cyclic hemiacetals are often more stable than their open-chain forms.

The Cyclic Hemiacetal Form of Glucose Aldoses contain an aldehyde group and several hydroxyl groups. The solid, crystalline form of an aldose is normally a cyclic hemiacetal. In solution, the aldose exists as an equilibrium mixture of the cyclic hemiacetal and the open-chain form. For most sugars, the equilibrium favors the cyclic hemiacetal.

Aldohexoses such as glucose can form cyclic hemiacetals containing either five-membered or six-membered rings. For most common aldohexoses, the equilibrium favors six-membered rings with a hemiacetal linkage between the aldehyde carbon and the hydroxyl group on C5. Figure 24-6 shows formation of the cyclic hemiacetal of glucose. Notice that the hemiacetal has a new asymmetric carbon atom at C1. Figure 24-6 shows the C1 hydroxyl group up, but another possible stereoisomer would have this hydroxyl group directed down.

The cyclic structure is often drawn initially in the **Haworth projection**, which depicts the ring as being flat (of course, it is not). The Haworth projection is widely used in biology texts, but most chemists prefer to use the more realistic chair conformation. Figure 24-6 shows the cyclic form of glucose both as a Haworth projection and as a chair conformation.

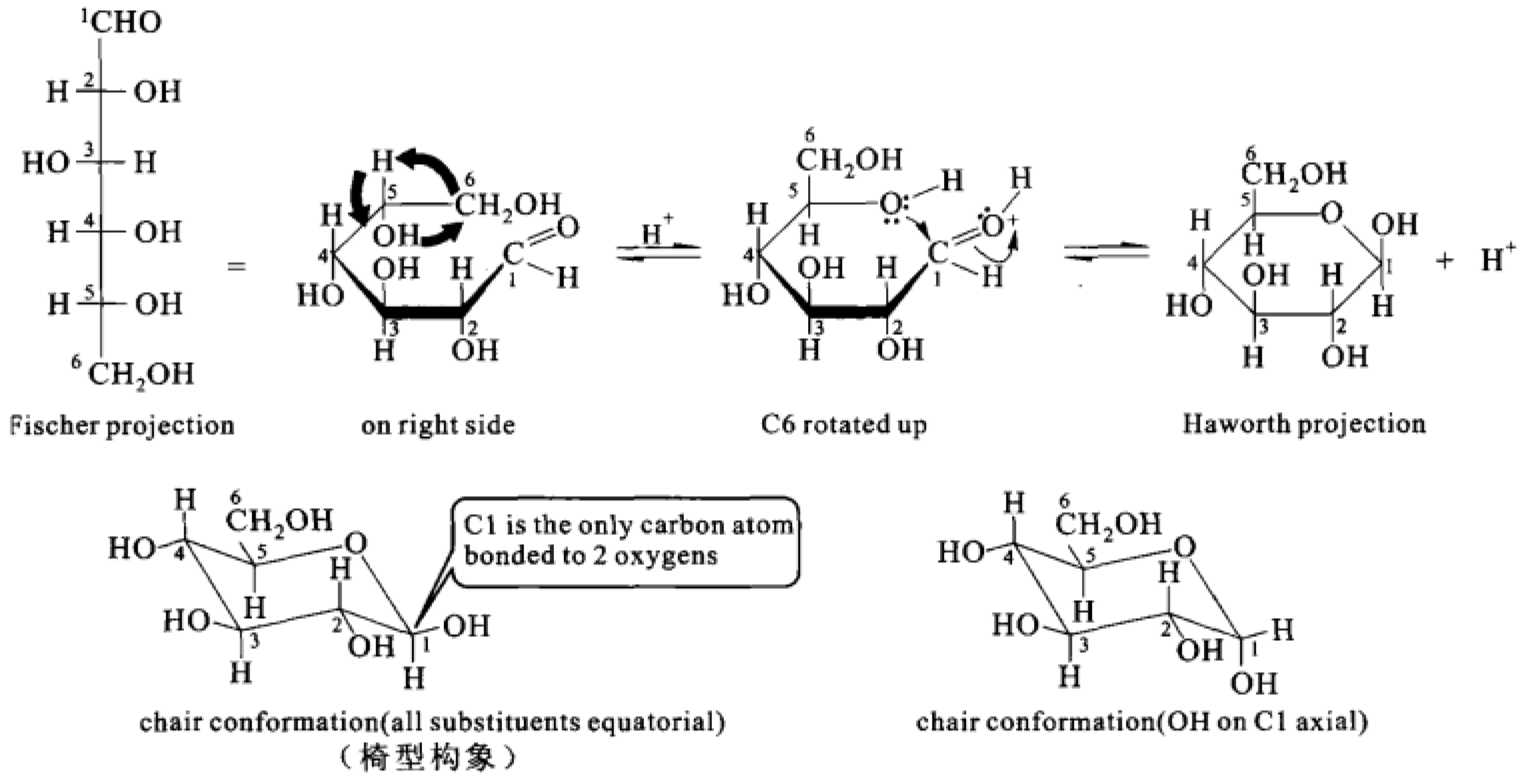


Figure 24-6 Glucose exists almost entirely as its cyclic hemiacetal form.

The Five-Membered Cyclic Hemiacetal Form of Fructose Not all sugars exist as six-membered rings in their hemiacetal forms. Many aldopentoses and ketohexoses form five-membered rings. The five-membered ring of fructose is shown in Figure 24-7, Five-membered rings are not puckered as much as six-membered rings, so they are usually depicted as flat Haworth projections. The five-membered ring is customarily drawn with the ring oxygen in back and the hemiacetal carbon (the one bonded to two oxygens) on the right. The —CH_2OH at the back left (C6) is in the up position for D-series ketohexoses.

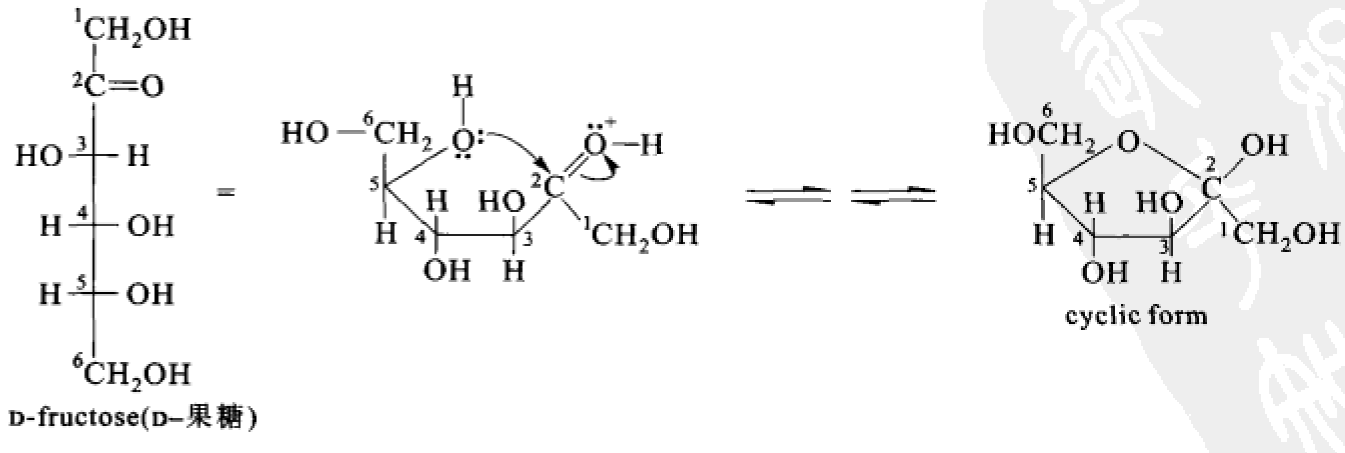
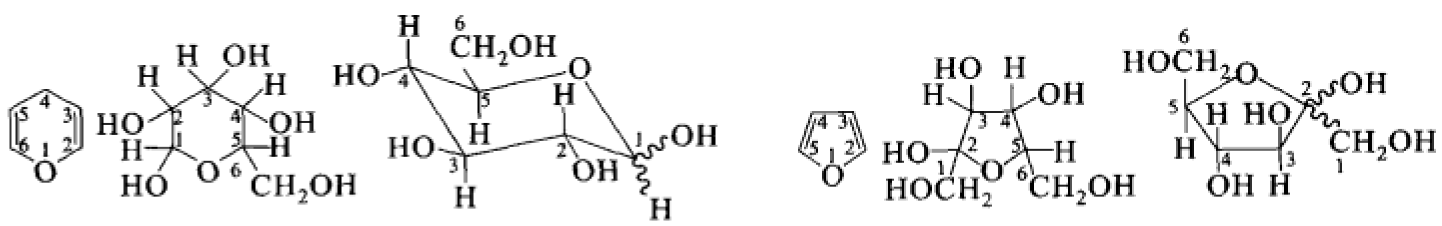


Figure 24-7 Fructose forms a five-membered cyclic hemiacetal. Five-membered rings are usually represented as flat Haworth structures.

Pyranose and Furanose Names Cyclic structures of monosaccharides are named according to their five- or six-membered rings. A six-membered cyclic hemiacetal is called a **pyranose**, derived from the name of the six-membered cyclic ether *pyran*. A five-membered cyclic hemiacetal is called a **furanose**, derived from the name of the five-membered cyclic ether *furan*. The ring is still numbered as it is in the sugar, not beginning with the heteroatom as it would be in the heterocyclic nomenclature. These structural names are incorporated into the systematic names of sugars.

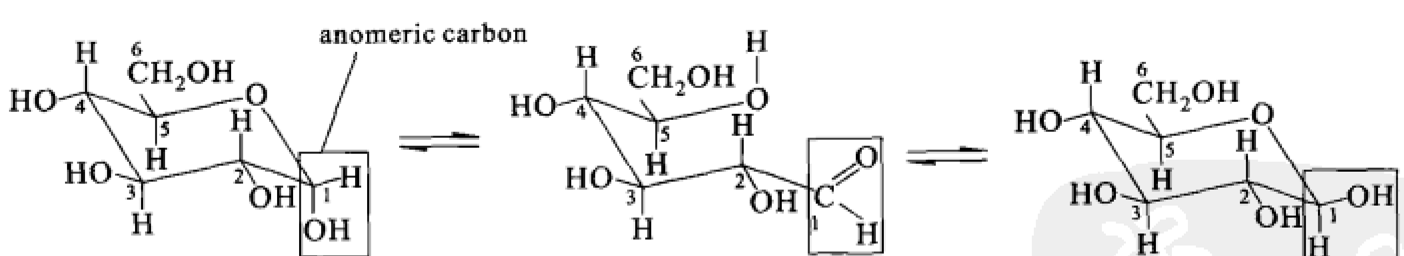


pyran (吡喃) a pyranose (吡喃糖) D-glucopyranose (D-吡喃型葡萄糖) furan (呋喃) a furanose (呋喃糖) D-fructofuranose (D-呋喃型葡萄糖)

24-7 Anomers of Monosaccharides; Mutarotation

When a pyranose or furanose ring closes, the hemiacetal carbon atom is converted from a flat carbonyl group to an asymmetric carbon. Depending on which face of the (protonated) carbonyl group is attacked, the hemiacetal —OH group can be directed either up or down. These two orientations of the hemiacetal —OH group give diastereomeric products called **anomers**. Figure 24-8 shows the anomers of glucose.

The hemiacetal carbon atom is called the **anomeric carbon**, easily identified as the only carbon atom bonded to two oxygens. Its —OH group is called the anomeric hydroxyl group. Notice in Figure 24-8 that the anomer with the anomeric —OH group down (axial) is called the α (alpha) anomer, and the one with the anomeric —OH group up (equatorial) is called the β (beta) anomer. We can draw the α and β anomers of most aldohexoses by remembering that the β form of glucose (β-D-glucopyranose) has all its substituents in equatorial positions. To draw an α anomer, simply move the anomeric —OH group to the axial position.



α-D-glucopyranose (α-D-吡喃型葡萄糖) open-chain form β-D-glucopyranose (β-D-吡喃型葡萄糖)

Figure 24-8 The anomers of glucose.

Another way to remember the anomers is to notice that the α anomer has its anomeric hydroxyl group trans to the terminal $—CH_2OH$ group, but it is cis in the β another. This rule works for all sugars, from both the D and L series, as well as for furanoses. Figure 24-9 shows the two anomers of fructose, whose anomeric carbon is C2. The α anomer has the anomeric —OH group down, trans to the terminal $—CH_2OH$ group, while the β anomer has it up, cis to the terminal $—CH_2OH$.

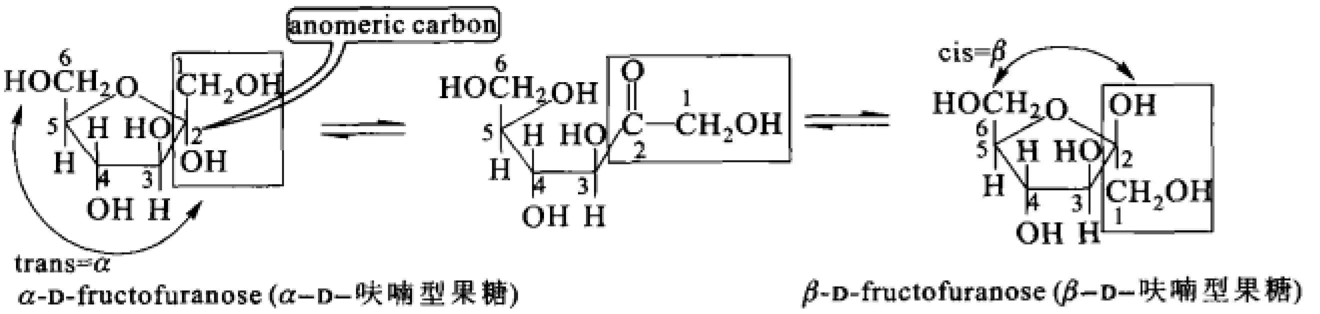


Figure 24-9 The α anomer of fructose has the anomeric —OH group down, trans to the terminal —CH_2OH group. The β anomer has the anomeric hydroxyl group up, cis to the terminal —CH_2OH.

PROBLEM 24-6

Draw the following monosaccharides, using chair conformations for the pyranoses and Haworth projections for the furanoses.

(a) α-D-mannopyranose (C2 epimer of glucose)

(b) β-D-galactopyranose (C4 epimer of glucose)

(c) β-D-allopyranose (C3 epimer of glucose)

(d) α-D-arabinofuranose

(e) β-D-ribofuranose (C2 epimer of arabinose)

Properties of Anomers: Mutarotation Because anomers are diastereomers, they generally have different properties. For example, α-D-glucopyranose has a melting point of 146 ℃ and a specific rotation of +112.2°, while β-D-glucopyranose has a melting point of 150 ℃ and a specific rotation of +18.7°. When glucose is crystallized from water at room temperature, pure crystalline α-D-glucopyranose results. If glucose is crystallized from water by letting the water evaporate at a temperature above 98 ℃, crystals of pure β-D-glucopyranose are formed (Figure 24-10).

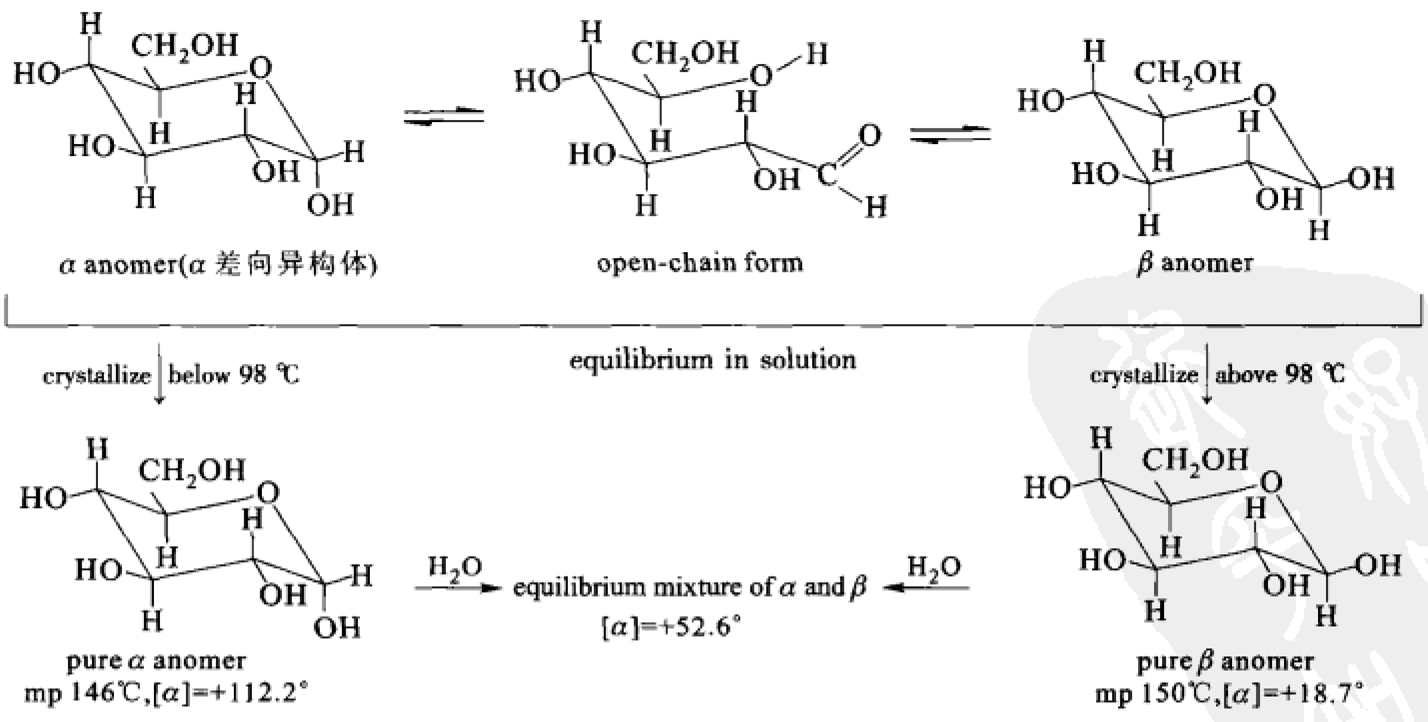


Figure 24-10 An aqueous solution of D-glucose contains an equilibrium mixture of α-D-glucopyranose, β-D-glucopyranose, and the intermediate open-chain form. Crystallization below 98 ℃ gives the α anomer, and crystallization above 98 ℃ gives the β anomer.

In each of these cases, *all* the glucose in the solution crystallizes as the favored anomer. In the solution, the two anomers are in equilibrium through a small amount of the open-chain form, and this equilibrium continues to supply more of the anomer that is crystallizing out of solution.

When one of the pure glucose anomers dissolves in water, an interesting change in the specific rotation is observed. When the α anomer dissolves, its specific rotation gradually decreases from an initial value of $+112.2°$ to $+52.6°$. When the pure β anomer dissolves, its specific rotation gradually increases from $+18.7°$ to the same value of $+52.6°$. This change ("mutation") in the specific rotation is called **mutarotation**. Mutarotation occurs because the two anomers interconvert in solution. When either of the pure anomers dissolves in water, its rotation gradually changes to an intermediate rotation that results from equilibrium concentrations of the anomers. The specific rotation of glucose is usually listed as $+52.6°$, the value for the equilibrium mixture of anomers. The positive sign of this rotation is the source of the name **dextrose**, an old common name for glucose.

24-8 Reactions of Monosaccharides: Side Reactions in Base

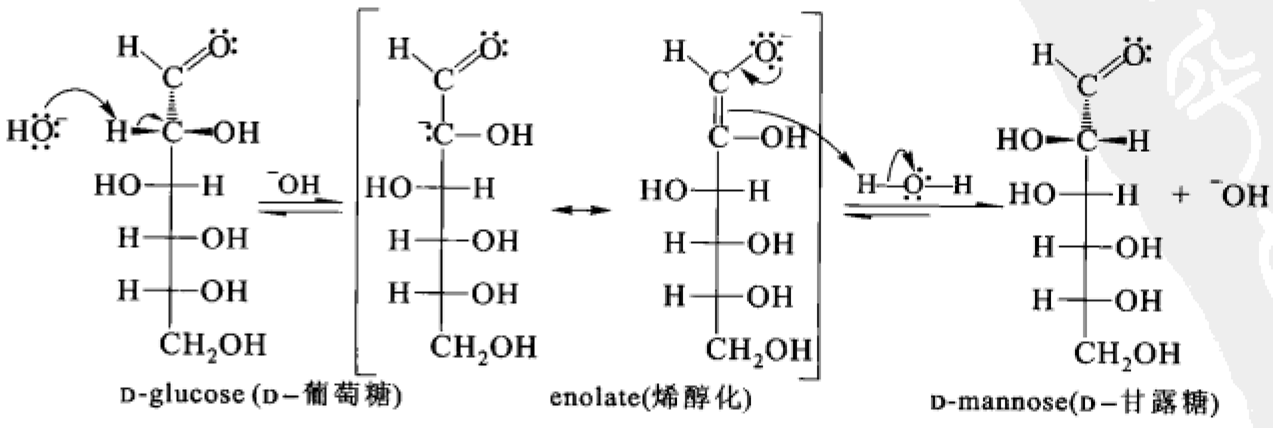
Sugars are multifunctional compounds that can undergo reactions typical of any of their functional groups. Most sugars exist as cyclic hemiacetals, yet in solution they are in equilibrium with their open-chain aldehyde or ketone forms. As a result, sugars undergo most of the usual reactions of ketones, aldehydes, and alcohols. Reagents commonly used with monofunctional compounds often give unwanted side reactions with sugars, however. Carbohydrate chemists have developed reactions that work well with sugars while avoiding the undesired side reactions. As we learn about the unique reactions of simple sugars, we will often draw them as their open-chain forms because it is often the small equilibrium amount of the open-chain form that reacts.

Epimerization and the Enediol Rearrangement One of the most important aspects of sugar chemistry is the inability, in most cases, to use basic reagents because they cause unwanted side reactions. Two common base-catalyzed side reactions are epimerization and enediol rearrangement.

Under basic conditions, the proton alpha to the aldehyde (or ketone) carbonyl group is reversibly removed (shown in the following Mechanism Box 24-1. In the resulting enolate ion, C2 is no longer asymmetric, and its stereochemistry is lost. Reprotonation can occur on either face of the enolate, giving either configuration. The result is an equilibrium mixture of the original sugar and its C2 epimer. Because a mixture of epimers results, this stereochemical change is called **epimerization.** The mechanism involves rapid base-catalyzed equilibration of glucose to a mixture of glucose and its C2 epimer, mannose.

MECHANISM 24-1 Base-Catalyzed Epimerization of Glucose

Step 1: Abstraction of the α proton. ***Step 2***: Reprotonation on the other face.



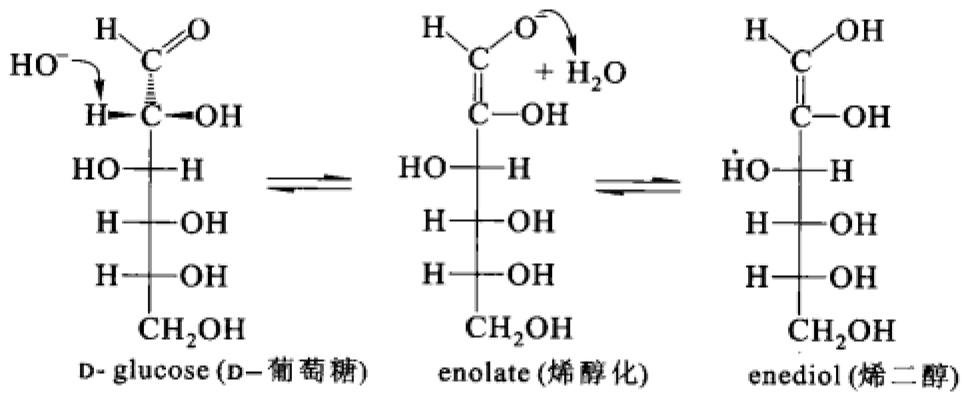
PROBLEM 24-7

Propose a mechanism for the base-catalyzed epimerization of erythrose to a mixture of erythrose and threose.

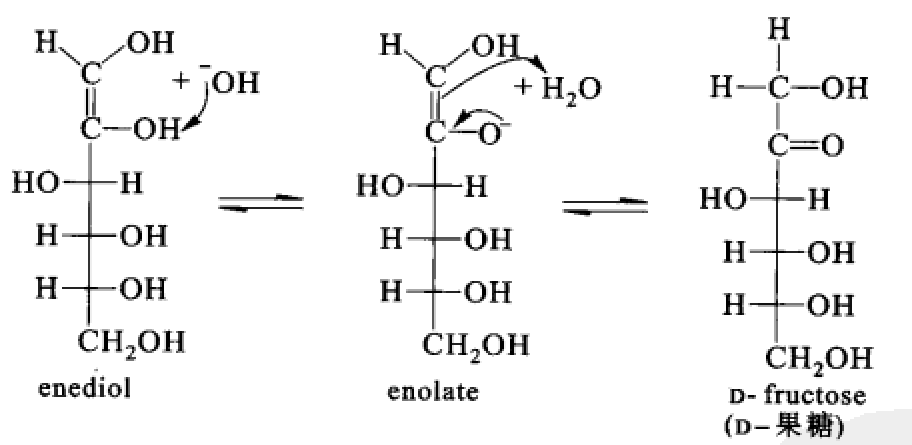
Another base-catalyzed side reaction is the **enediol rearrangement**, which moves the carbonyl group up and down the chain, as shown in the following Mechanism 24-2. If the enolate ion (formed by removal of a proton on C2) reprotonates on the C1 oxygen, an **enediol** intermediate results. Removal of a proton from the C2 oxygen and reprotonation on C1 gives fructose, a ketose.

MECHANISM 24-2 Base-Catalyzed Enediol Rearrangement

Step 1: Remove the α proton. ***Step 2***: Reprotonate on oxygen to give the enediol.



Step 3: Deprotonate the oxygen on C2. ***Step 4***: Reprotonate on C1 to give the ketose.



Under strongly basic conditions, the combination of enediol rearrangements and epimerization leads to a complex mixture of sugars. Except when using protected sugars, most chemists doing sugar chemistry employ neutral or acidic reagents to avoid these annoying side reactions.

PROBLEM 24-8

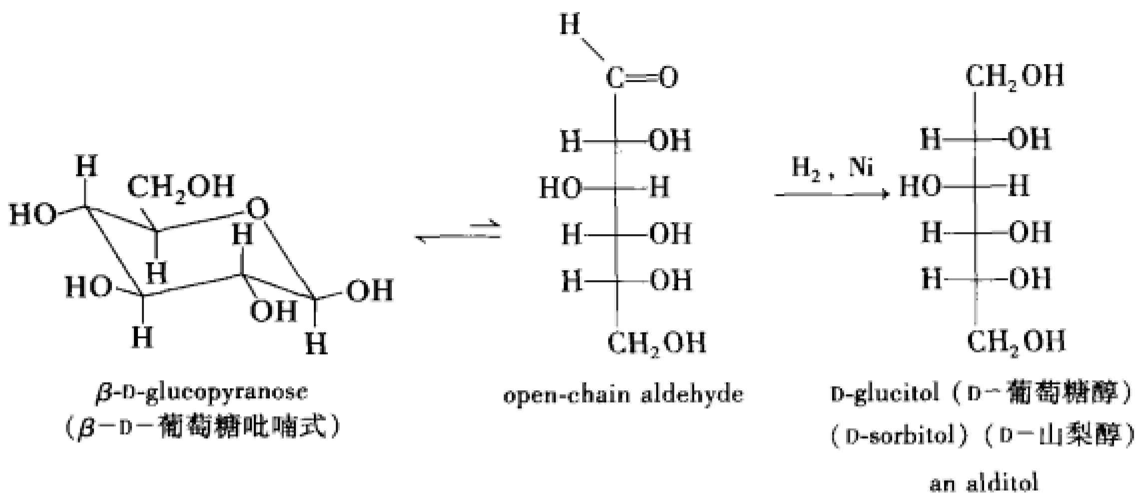
Show how C3 of fructose can epimerize under basic conditions.

PROBLEM 24-9

Show how another enediol rearrangement can move the carbonyl group from C2 in fructose to C3.

24-9 Reduction of Monosaccharides

Like other aldehydes and ketones, aldoses and ketoses can be reduced to the corresponding polyalcohols, called **sugar alcohols** or **alditols**. The most common reagents are sodium borohydride or catalytic hydrogenation using a nickel catalyst. Alditols are named by adding the suffix-*itol* to the root name of the sugar. The following equation shows the reduction of glucose to glucitol, sometimes called *sorbitol*.



Reduction of a ketose creates a new asymmetric carbon atom, formed in either of two configurations, resulting in two epimers. Figure 24-11 shows how the reduction of fructose gives a mixture of glucitol and mannitol.

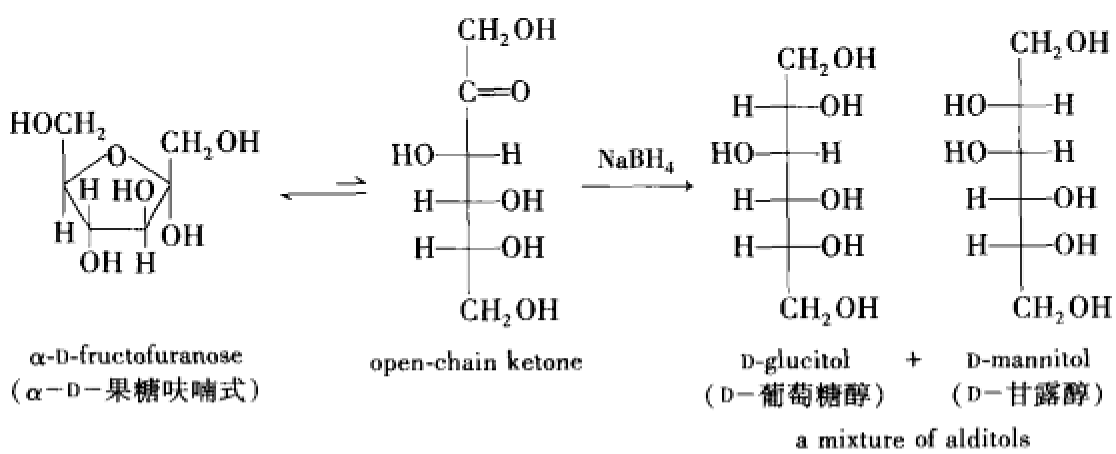


Figure 24-11 Reduction of fructose creates a new asymmetric carbon atom, which can have either configuration. The products are a mixture of glucitol and mannitol.

Sugar alcohols are widely used in industry, primarily as food additives and sugar substitutes. Glucitol has the common name *sorbitol* because it was first isolated from the berries of the mountain ash, *Sorbus aucuparia*. Industrially, sorbitol is made by catalytic hydrogenation of glucose. Sorbitol is used as a sugar substitute, a moistening agent, and a starting material for making vitamin C. Mannitol was first isolated from plant exudates known as *mannas* (of Biblical fame), the origin of the names *mannose* and *mannitol*. Mannitol is derived commercially from seaweed, or it can be made by catalytic hydrogenation of mannose. Galactitol (*dulcitol*) also can be obtained from many plants, or it can be made by catalytic hydrogenation of galactose.

PROBLEM 24-10

When D-glucose is treated with sodium borohydride, optically active glucitol results. When optically active D-galactose is reduced, however, the product is optically inactive. Explain this loss of optical activity.

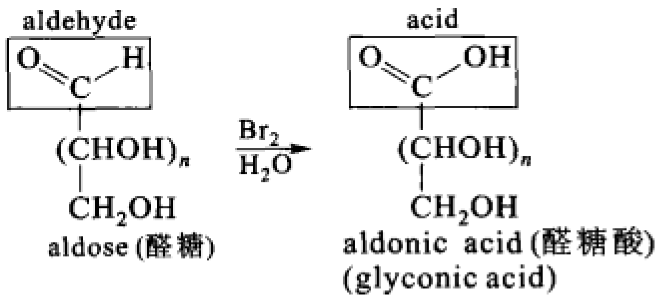
PROBLEM 24-11

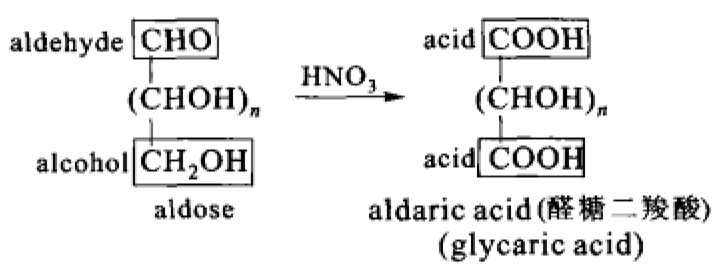
Emil Fischer synthesized L-gulose, an unusual aldohexose that reduces to give D-glucitol. Suggest a structure for this L sugar, and show how L-gulose gives the same alditol as D-glucose. (*Hint*: D-Glucitol has $—CH_2OH$ groups at both ends. *Either* of these primary alcohol groups might have come from reduction of an aldehyde.)

24-10 Oxidation of Monosaccharides; Reducing Sugars

Monosaccharides are oxidized by a variety of reagents. The aldehyde group of an aldose oxidizes easily. Some reagents also selectively oxidize the terminal $—CH_2OH$ group at the far end of the molecule. Oxidation is used to identify the functional groups of a sugar, to help to determine its stereochemistry, and as part of a synthesis to convert one sugar into another.

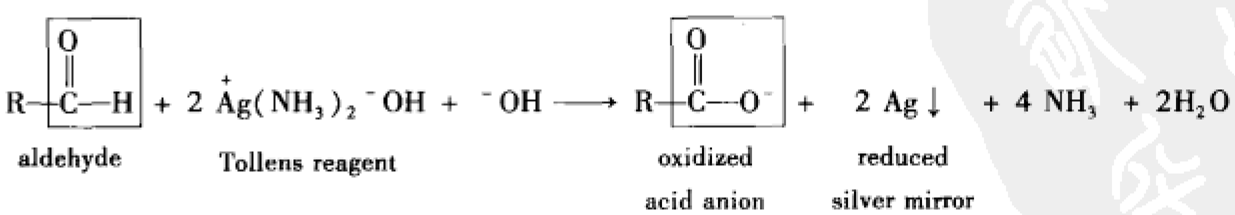
Bromine Water Bromine water oxidizes the aldehyde group of an aldose to a carboxylic acid. Bromine water is used for this oxidation because it does not oxidize the alcohol groups of the sugar and it does not oxidize ketoses. Also, bromine water is acidic and does not cause epimerization or rearrangement of the carbonyl group. Because bromine water oxidizes aldoses but not ketoses, it serves as a useful test to distinguish aldoses from ketoses. The product of bromine water oxidation is an **aldonic acid** (older term: glyconic acid). For example, bromine water oxidizes glucose to gluconic acid.



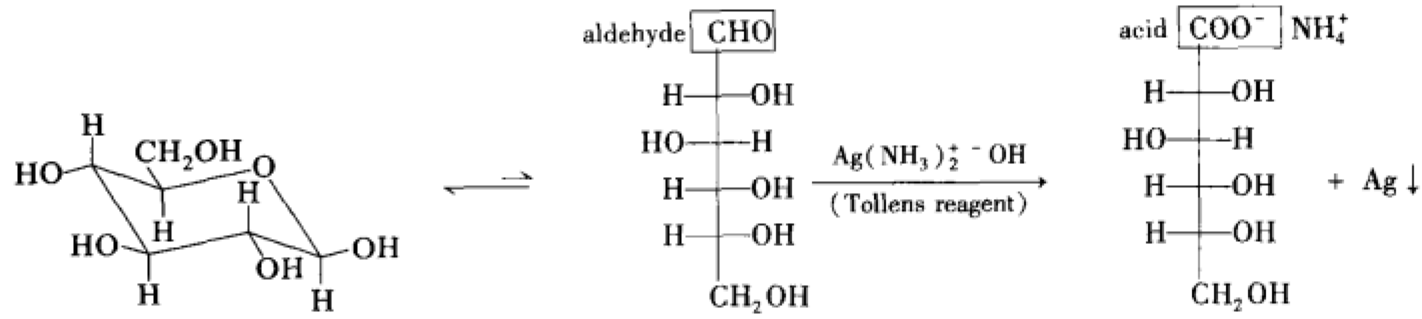


Nitric Acid Nitric acid is a stronger oxidizing agent than bromine water, oxidizing both the aldehyde group and the terminal $—CH_2OH$ group of an aldose to carboxylic acid groups. The resulting dicarboxylic acid is called an **aldaric acid** (older terms: **glycaric acid** or **saccharic acid**). For example, nitric acid oxidizes glucose to glucaric acid.

Tollens Test **Tollens test** detects aldehydes, which react with Tollens reagent to give carboxylate ions and metallic silver, often in the form of a silver mirror on the inside of the container.

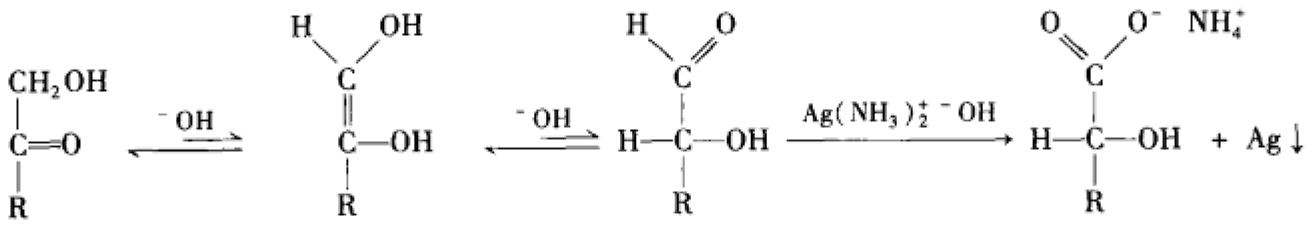


In its open-chain form, an aldose has an aldehyde group, which reacts with Tollens reagent to give an aldonic acid and a silver mirror. This oxidation is not a good synthesis of the aldonic acid, however, because Tollens reagent is strongly basic and promotes epimerization and enediol rearrangements. Sugars that reduce Tollens reagent to give a silver mirror are called **reducing sugars**.



β-D-glucose (β-D-葡萄糖) open-chain form gluconic acid (葡萄糖酸) (+ side products)

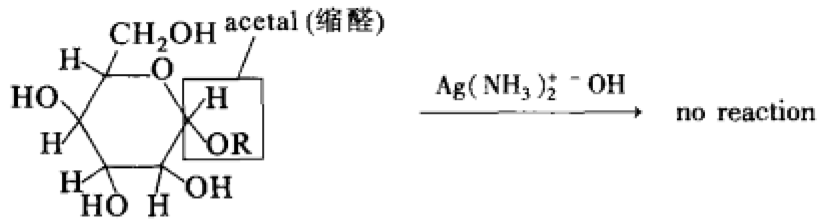
Tollens test cannot distinguish between aldoses and ketoses because the basic Tollens reagent promotes enediol rearrangements. Under basic conditions, the open-chain form of a ketose can isomerize to an aldose, which reacts to give a positive Tollens test.



a ketose (酮糖) enediol intermediate (烯二醇中间体) an aldose (醛糖) positive Tollens test

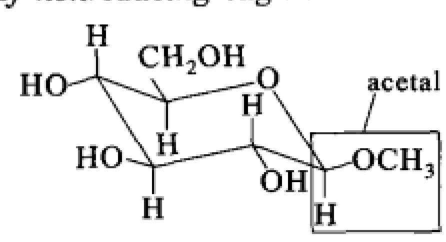
24-11 Nonreducing Sugars: Formation of Glycosides

What good is Tollens test if it doesn't distinguish between aldoses and ketoses? The answer lies in the fact that Tollens reagent must react with the open-chain form of the sugar, which has a free aldehyde or ketone. If the cyclic form cannot open to the free carbonyl compound, the sugar does not react with Tollens reagent. Hemiacetals are easily opened, but an acetal is stable under neutral or basic conditions. If the carbonyl group is in the form of a cyclic acetal, the cyclic form cannot open to the free carbonyl compound, and the sugar gives a negative Tollens test.

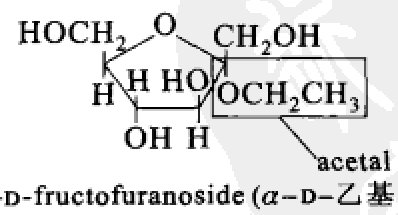


a glycoside (苷, 配糖物)

Examples of nonreducing sugars



methyl β-D-glucopyranoside (β-D-甲基吡喃型葡萄糖苷) (or methyl β-D-glucoside)



ethyl α-D-fructofuranoside (α-D-乙基呋喃型果糖苷) (or ethyl α-D-fructoside)

Sugars in the form of acetals are called **glycosides**, and their names end in the *-oside* suffix. For example, a glycoside of glucose would be a **glucoside**, and if it were a six-membered ring, it would be a *glucopyranoside*. Similarly, a glycoside of ribose would be a *riboside*, and if it were a five-membered ring, it would be a *ribofuranoside*. In general, a sugar whose name ends with the suffix *-ose* is a reducing sugar, and one whose name ends with *-oside* is nonreducing. Because they exist as stable acetals rather than hemiacetals, glycosides cannot spontaneously open to their open-chain forms, and they do not mutarotate. They are locked in a particular ano-

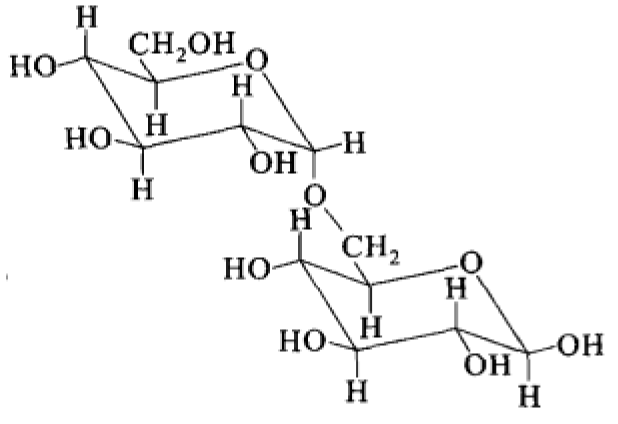
meric form.

We can summarize by saying that Tollens test distinguishes between reducing sugars and nonreducing sugars: Reducing sugars (aldoses and ketoses) are hemiacetals, and they mutarotate. Nonreducing sugars (glycosides) are acetals, and they do not mutarotate.

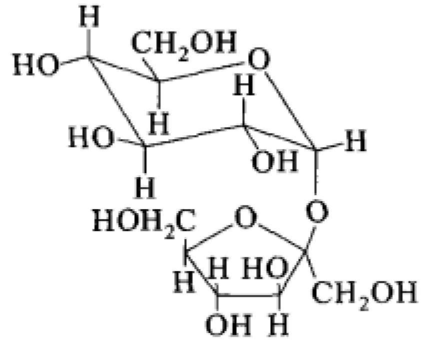
PROBLEM 24-12

Which of the following are reducing sugars? Comment on the common name *sucrose* for table sugar.

(a) methyl α-D-galactopyranoside
(b) β-L-idopyranose (an aldohexose)
(c) α-D-allopyranose
(d) ethyl β-D-ribofuranoside
(e)

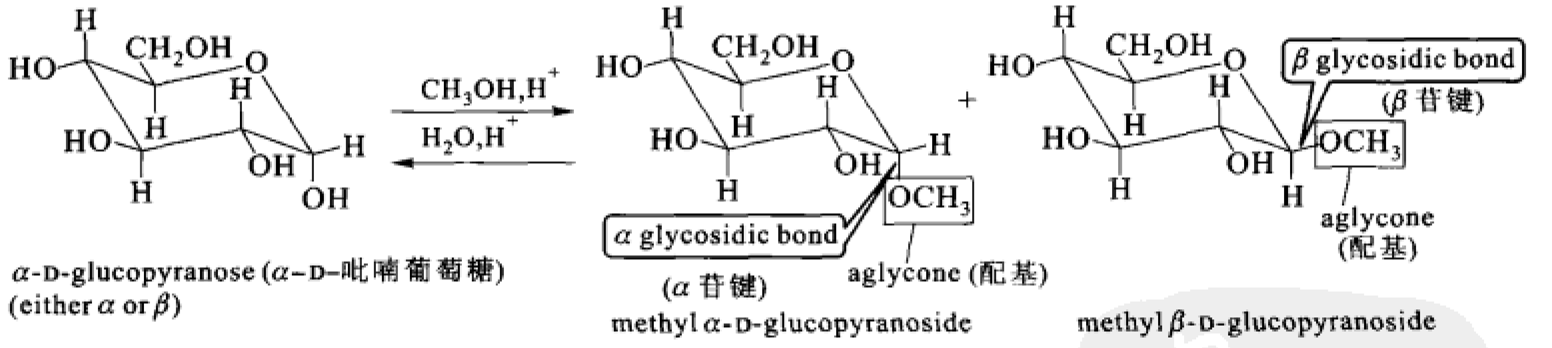


(f)



sucrose (蔗糖)

Formation of Glycosides Recall that aldehydes and ketones are converted to acetals by treatment with an alcohol and a trace of acid catalyst. These conditions also convert aldoses and ketoses to the acetals we call glycosides. Regardless of the anomer used as the starting material, both anomers of the glycoside are formed (as an equilibrium mixture) under these acidic conditions. The more stable anomer predominates. For example, the acid-catalyzed reaction of glucose with methanol gives a mixture of methyl glucosides.

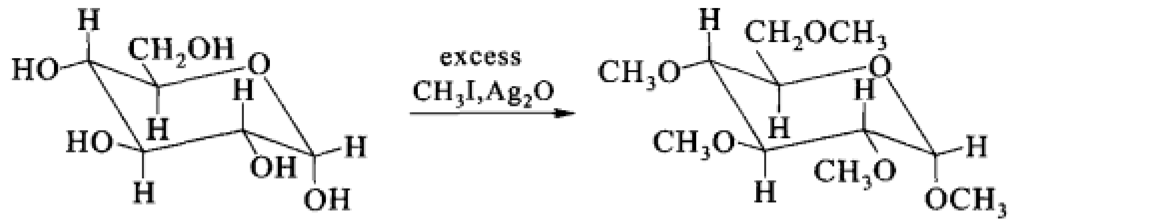


Like other acetals, glycosides are stable to basic conditions, but they hydrolyze in aqueous acid to a free sugar and an alcohol. Glycosides are stable with basic reagents and in basic solutions.

24-12 Ether and Ester Formation

Because they contain several hydroxyl groups, sugars are very soluble in water and rather insoluble in organic solvents. Sugars are difficult to recrystallize from water because they often form supersaturated syrups like honey and molasses. If the hydroxyl groups are alkylated to form ethers, sugars behave like simpler organic compounds. The ethers are soluble in organic solvents, and they are more easily purified by recrystallization and simple chromatographic methods.

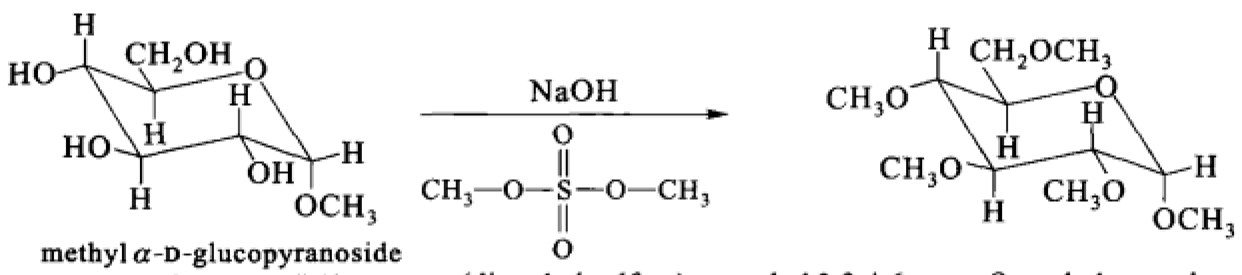
Treating a sugar with methyl iodide and silver oxide converts its hydroxyl groups to methyl ethers. Silver oxide polarizes the H_3C—I bond, making the methyl carbon strongly electrophilic. Attack by the carbohydrate —OH group, followed by deprotonation, gives the ether. The anomeric hydroxyl group is also converted to an ether. If the conditions are carefully controlled, the hemiacetal C—O bond is not broken, and the configuration at the anomeric carbon is preserved.



α-D-glucopyranose

methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside
(2,3,4,6–四–*O*–甲基–α–D–甲基吡喃葡萄糖苷)

The Williamson ether synthesis is the most common method for forming simple ethers, but it involves a strongly basic alkoxide ion. Under these basic conditions, a simple sugar would isomerize and decompose. A modified Williamson method may be used if the sugar is first converted to a glycoside (by treatment with an alcohol and an acid catalyst). The glycoside is an acetal, stable to base. Treatment of a glycoside with sodium hydroxide and methyl iodide or dimethyl sulfate gives the methylated carbohydrate.

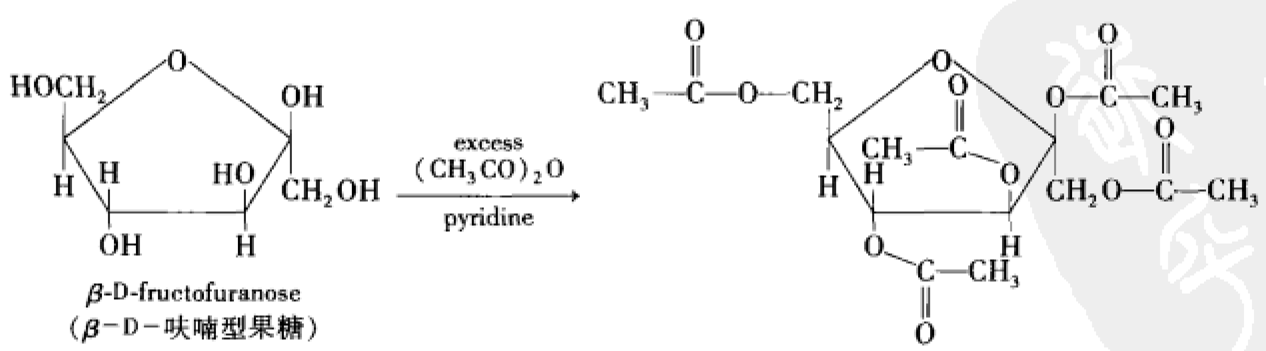


methyl α-D-glucopyranoside
(α–D–甲基吡喃,葡萄糖苷)
(stable to base)

(dimethyl sulfate)

methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside

Ester Formation Another way to convert sugars to easily handled derivatives is to acylate the hydroxyl groups to form esters. Sugar esters are readily crystallized and purified, and they dissolve in common organic solvents. Treatment with acetic anhydride and pyridine (as a mild basic catalyst) converts sugar hydroxyl groups to acetate esters. This reaction acetylates all the hydroxyl groups, including that of the hemiacetal on the anomeric carbon. The anomeric C—O bond is not broken in the acylation, and the stereochemistry of the anomeric carbon atom is usually preserved. If we start with a pure α anomer or a pure β anomer, the product is the corresponding anomer of the acetate.



β-D-fructofuranose
(β–D–呋喃型果糖)

penta-*O*-acetyl-β-D-fructofuranoside
(五–*O*–乙酰基–β–D–呋喃型果糖苷)

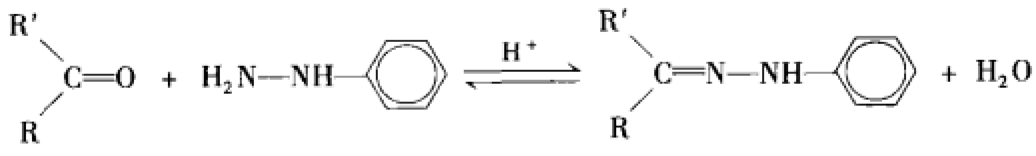
PROBLEM 24-13

Predict the products formed when the following sugars react with acetic anhydride and pyridine.

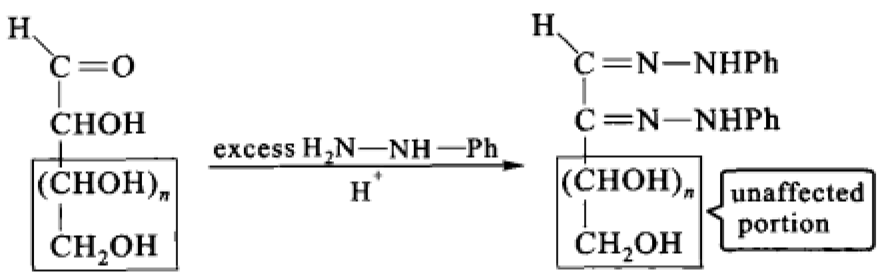
(a) α-D-glucopyranose (b) β-D-ribofuranose

24-13 Reactions with Phenylhydrazine: Osazone Formation

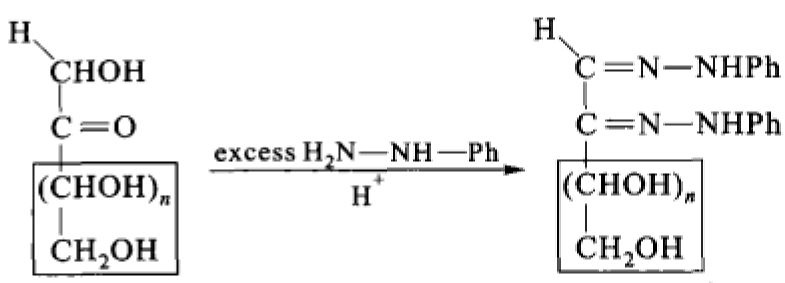
Before spectroscopy, one of the best ways to identify ketones and aldehydes was conversion to crystalline hydrazones, especially phenylhydrazones and 2,4-dinitrophenylhydrazones. In his exploratory work on sugar structures, Emil Fischer often made and used phenylhydrazone derivatives. In fact, his constant use of phenylhydrazine ultimately led to Fischer's death in 1919 from chronic phenylhydrazine poisoning.



Sugars do not form the simple phenylhydrazone derivatives we might expect, however. Two molecules of phenylhydrazine condense with each molecule of the sugar to give an **osazone**, in which both C1 and C2 have been converted to phenylhydrazones. The term *osazone* is derived from the *-ose* suffix of a sugar and the last half of the word hydr*azone*. Most osazones are easily crystallized, with sharp melting points. Melting points of osazone derivatives provide valuable clues for the identification and comparison of sugars.



aldose(醛糖) osazone(脎)



ketose(酮糖) osazone(脎)

In the formation of an osazone, both C1 and C2 are converted to phenylhydrazones. Therefore, a ketose gives the same osazone as its related aldose. Also notice that the stereochemistry at C2 is lost in the phenylhydrazone. Thus, C2 epimers give the same osazone.

PROBLEM 24-14

(a) Show that D-glucose, D-mannose and D-fructose all give the same osazone. Show the structure and stereochemistry of this osazone.

(b) D-Talose is an aldohexose that gives the same osazone as D-galactose. Give the structure of D-talose, and give the structure of its osazone.

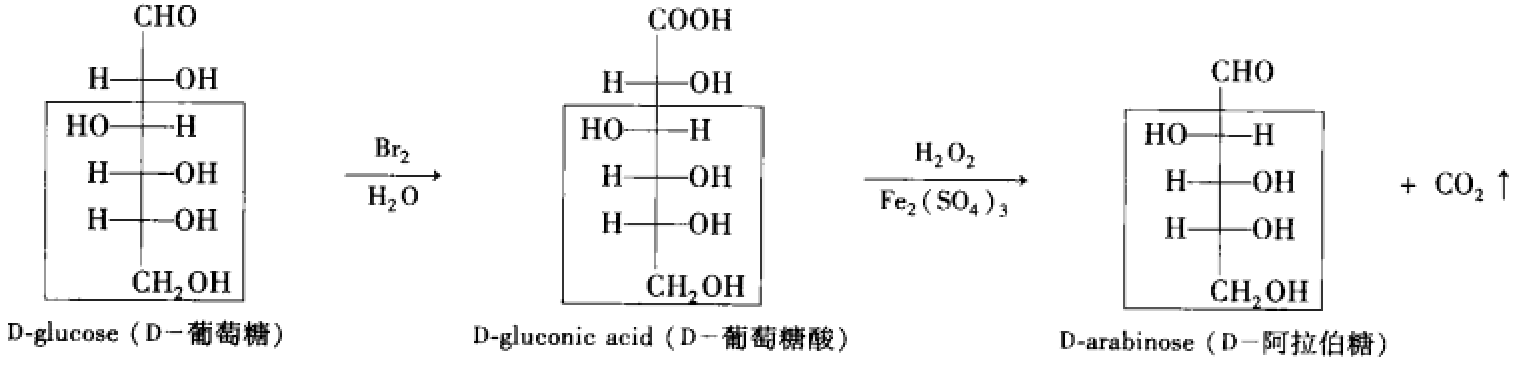
24-14 Chain Shortening: The Ruff Degradation

In our discussion of D and L sugars, we briefly mentioned a method for shortening the chain of an aldose by remo-

ving the aldehyde carbon at the top of the Fischer projection. Such a reaction, removing one of the carbon atoms, is called a **degradation.**

The most common method used to shorten sugar chains is the **Ruff degradation**, developed by Otto Ruff, a prominent German chemist around the turn of the twentieth century. The Ruff degradation is a two-step process that begins with a bromine-water oxidation of the aldose to its aldonic acid. Treatment of the aldonic acid with hydrogen peroxide and ferric sulfate oxidizes the carboxyl group to CO_2 and gives an aldose with one less carbon atom. The Ruff degradation is used mainly for structure determination and synthesis of new sugars.

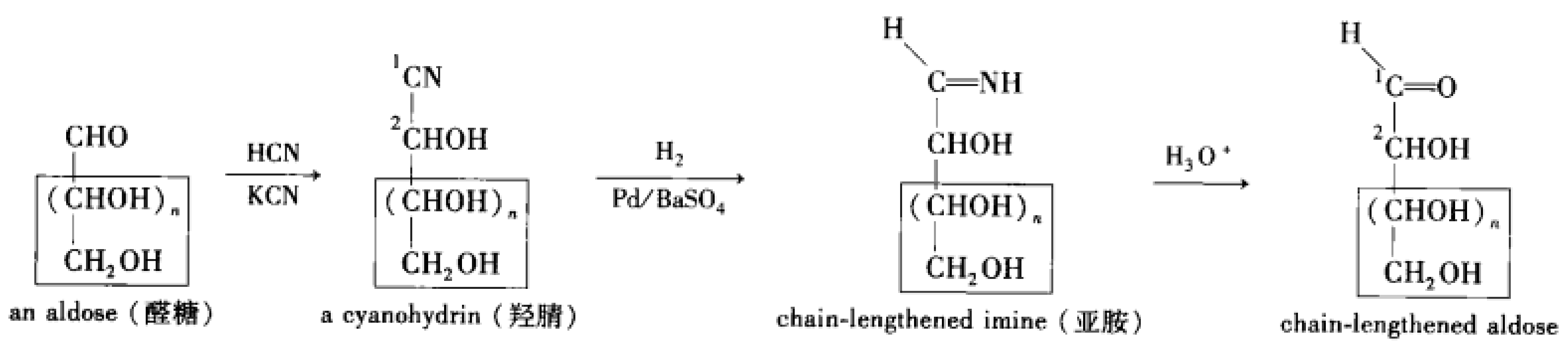
Ruff degradation (Ruff 降解)



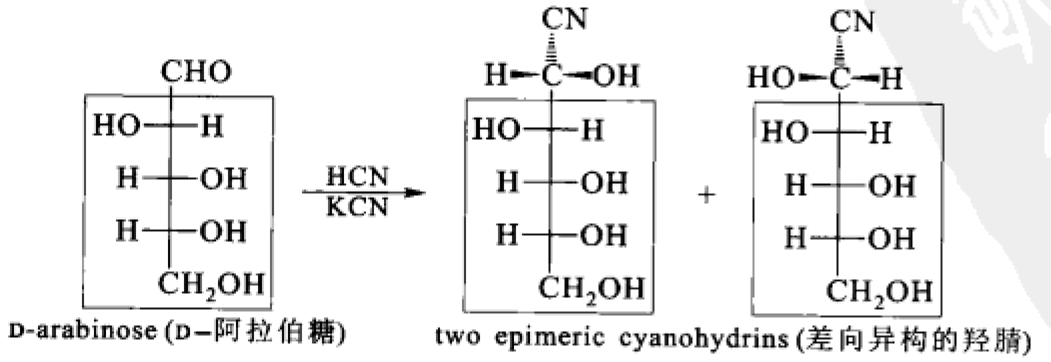
24-15 Chain Lengthening: The Kiliani-Fischer Synthesis

The **Kiliani-Fischer synthesis** lengthens an aldose carbon chain by adding one carbon atom to the aldehyde end of the aldose. The result of this process is a chain-lengthened sugar with a new carbon atom at C1 and the former aldehyde group (the former C1) now at C2. This synthesis is useful both for determining the structure of existing sugars and for synthesizing new sugars.

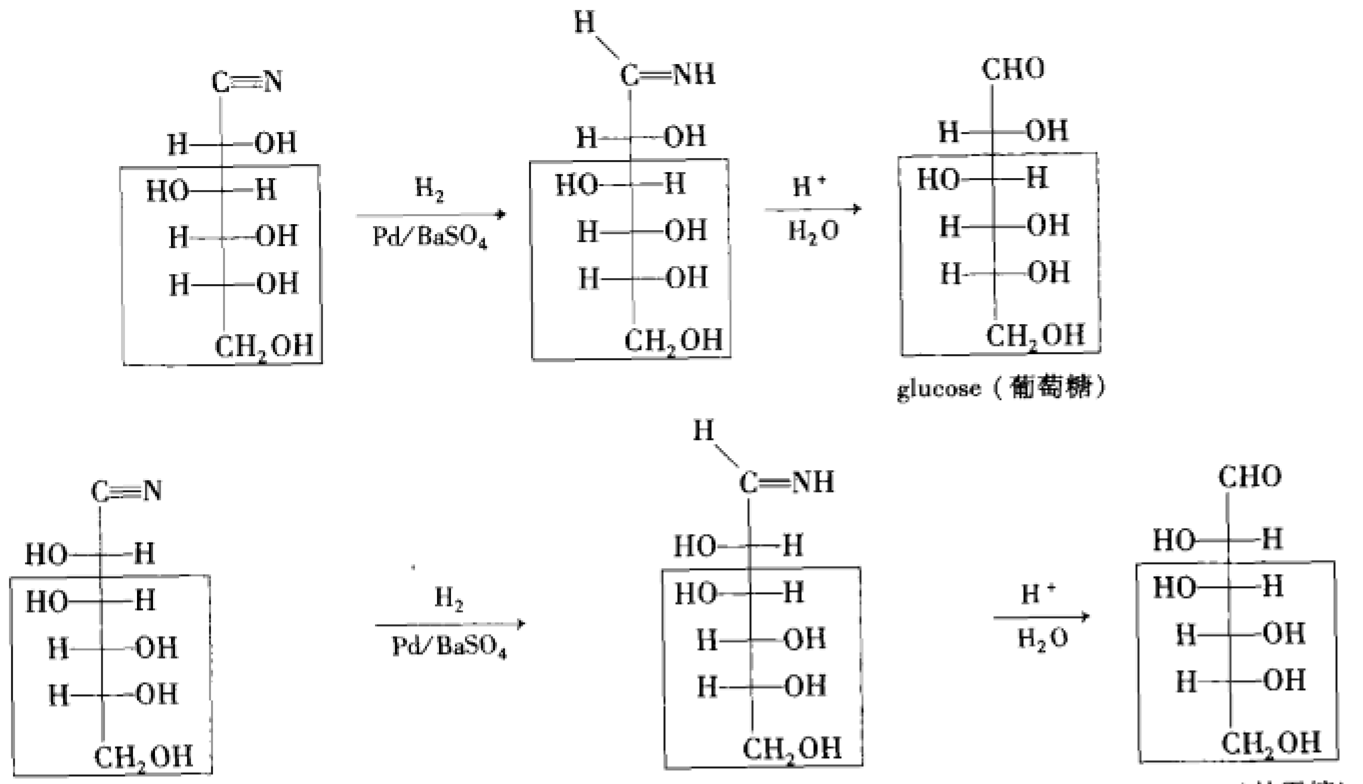
The Kiliani-Fischer synthesis



The aldehyde carbon atom is made asymmetric in the first step, formation of the cyanohydrin. Two epimeric cyanohydrins result. For example, D-arabinose reacts with HCN to give the following cyanohydrins.



Aqueous hydrogenation of these cyanohydrins gives two imines, which quickly hydrolyze to aldehydes. A poisoned catalyst of palladium on barium sulfate is used for the hydrogenation, to avoid overreduction.



epimeric cyanohydrins (差向异构羟腈) epimeric imines (差向异构亚胺) mannose (甘露糖)

The Kiliani-Fischer synthesis accomplishes the opposite of the Ruff degradation. Ruff degradation of either of two C2 epimers gives the same shortened aldose, and the Kiliani-Fischer synthesis converts this shortened aldose back into a mixture of the same two C2 epimers. For example, glucose and mannose are degraded to arabinose, and the Kiliani-Fischer synthesis converts arabinose into a mixture of glucose and mannose.

24−16 Fischer's Proof of the Configuration of Glucose

Considering the stereochemical complexity of sugars, it is amazing that Emil Fischer determined the structures of glucose and the other aldohexoses in 1891, only 14 years after the tetrahedral structure of carbon had been proposed. Fischer received the Nobel Prize for this work in 1902. Much of Fischer's proof used the carbohydrate reactions we have studied, together with some clever reasoning about the symmetry and dissymmetry of the resulting products. We will use Fischer's work with glucose as an elegant example of these reactions, showing the determination of complex stereochemistry by clever use of simple methods.

In 1891, there were no methods for determining the absolute configuration of molecules, so Fischer could not know which enantiomer was the naturally occurring one. He made the assumption that the —OH group on C2 of (+)-glyceraldehyde (and on the bottom asymmetric carbon of the D family of sugars) is on the right in the Fischer projection. Eventually, this was shown to be a correct guess, but all his reasoning would have applied to the other enantiomers if the guess had been wrong.

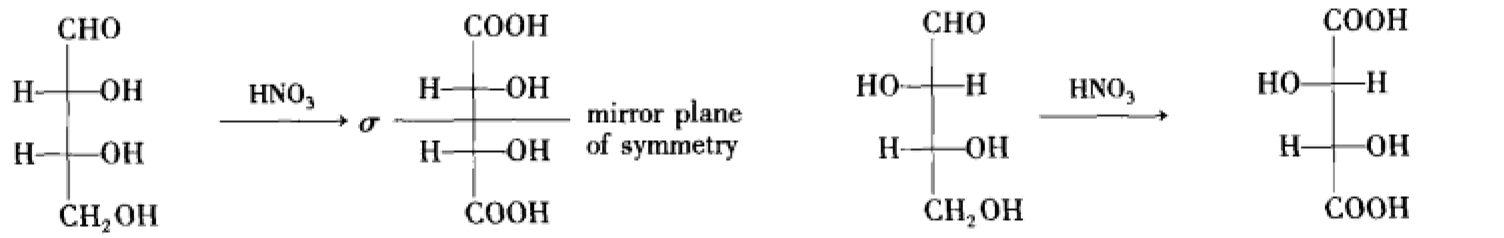
Fischer had done many chemical tests on glucose, and he had used Ruff degradations to degrade it to D-(+)-glyceraldehyde. He knew that glucose is an aldose and that it has six carbon atoms; therefore, the eight members of the D family of aldohexoses (Figure 24−3) are the possible structures. Fischer used four major clues to determine which of these structures corresponds to glucose. We will consider the four clues individually and study the information obtained from each.

CLUE 1: On Ruff degradation, glucose and mannose give the same aldopentose: D-(−)-arabinose.

This clue suggests that glucose and mannose are C2 epimers, a hypothesis he confirmed by treating them with phenylhydrazine and showing that glucose and mannose give the same osazone. Even more important, this information relates the structure of glucose to the simpler structure of arabinose, the chain-shortened aldopentose.

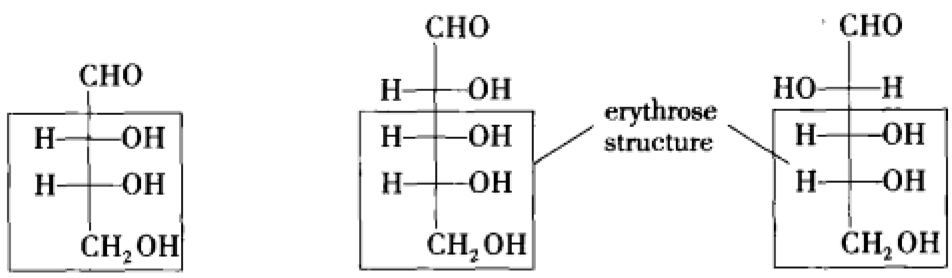
CLUE 2: On Ruff degradation, D-(−)-arabinose gives the aldotetrose D-(−)-erythrose. Upon treatment with nitric acid, erythrose gives an *optically inactive* aldaric acid, *meso*-tartaric acid.

D-Erythrose, obtained from Ruff degradation of a D-aldopentose, must be a D-aldotetrose. There are only two D-aldotetroses, labeled below as structures Ⅰ and Ⅱ. Nitric acid oxidation of structure Ⅰ gives a symmetrical meso product, but structure Ⅱ gives an optically active product.



structure Ⅰ (erythrose)(赤藓糖) — *meso*-tartaric acid (内消旋酒石酸) — structure Ⅱ — optically active tartaric acid (光学活性的酒石酸)

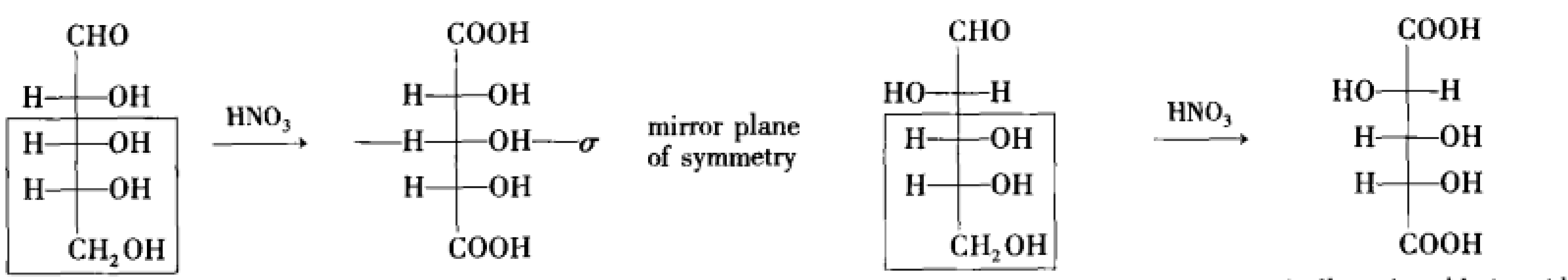
Because oxidation of D-erythrose gives an optically inactive aldaric acid, erythrose must correspond to structure Ⅰ. Structure Ⅰ would give *meso*-tartaric acid when it is oxidized to an aldaric acid. D-Arabinose must be one of the two epimeric structures that would degrade to this structure for D-erythrose.



D-(−)-erythrose (赤藓糖) — possible structures of D-(−)-arabinose (阿拉伯糖)

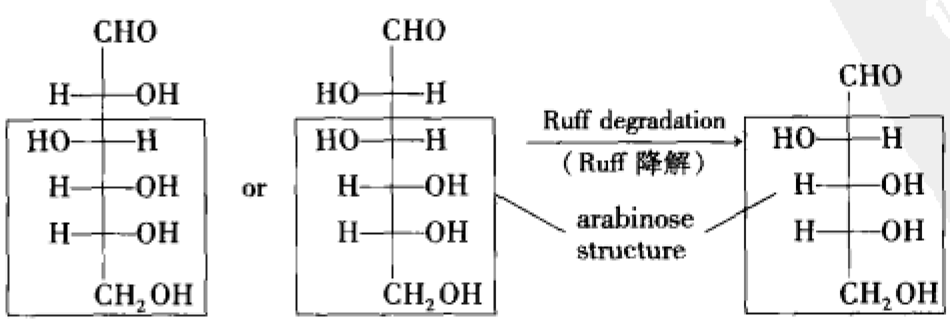
CLUE 3: On oxidation with nitric acid, D-(−)-arabinose gives an *optically active* aldaric acid.

Of the two possible structures for D-arabinose (below), only the second would oxidize to give an optically active aldaric acid. Structure B must be arabinose.



structure A — optically inactive aldaric acid (光学非活性糖二酸) — structure B (D-arabinose, D-阿拉伯糖) — optically active aldaric acid

Since glucose and mannose degrade to arabinose, structures X and Y shown below must be glucose and mannose. At this point, however, it is impossible to tell which structure is glucose and which is mannose.



structure X — structure Y — D-arabinose (D-阿拉伯糖)

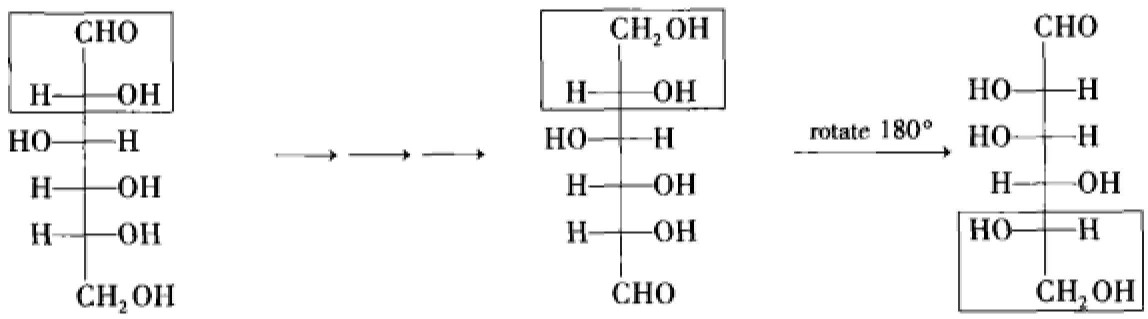
CLUE 4: When the —CHO and —CH_2OH groups of D-mannose are interchanged, the product is still D-mannose. When the —CHO and —CH_2OH groups of D-glucose are interchanged, the product is an unnatural L

sugar.

Fischer had developed a clever method for converting the aldehyde group of an aldose to an alcohol while converting the terminal alcohol group to an aldehyde. In effect, this synthesis interchanges the two end groups of the aldose chain.

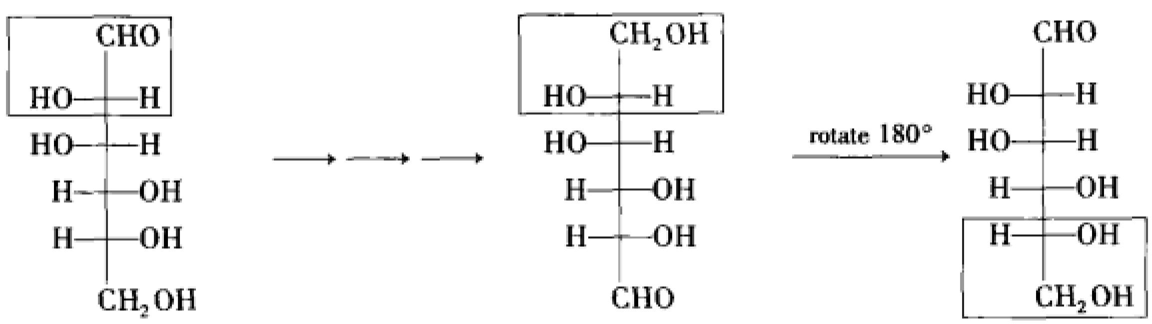
original aldose — end groups interchanged

If the two end groups of structure X are interchanged, the product looks strange indeed. Remember that we can rotate a Fischer projection by 180°; when we do that, it becomes clear that the product is an unusual sugar of the L series (L-gulose). Structure X must be D-glucose.



structure X (D-glucose) (D-葡萄糖) — end groups interchanged — an L sugar (L-gulose)

Structure Y gives a D sugar when its end groups are interchanged. In fact, a 180° rotation shows that the product of end-group interchange in structure Y gives back the original structure! Structure Y must be D-mannose.



structure Y (D-mannose) (D-甘露糖) — end groups interchanged — structure Y (D-mannose)

This type of reasoning can be used to determine the structures of all the other aldoses. Problems 24-15 and 24-16 will give you some practice determining sugar structures.

PROBLEM 24-15

On treatment with phenylhydrazine, aldohexoses **A** and **B** give the same osazone. On treatment with warm nitric acid, **A** gives an optically inactive aldaric acid, but sugar **B** gives an optically active aldaric acid. Sugars **A** and **B** are both degraded to aldopentose **C**, which gives an optically active aldaric acid on treatment with nitric acid. Aldopentose **C** is degraded to aldotetrose **D**, which gives optically active tartaric acid when it is treated with nitric acid. Aldotetrose **D** is degraded to (+)-glyceraldehyde. Deduce the structures of sugars **A**, **B**, **C**, and **D**, and use Figure 24-3 to determine the correct names of these sugars.

PROBLEM 24-16

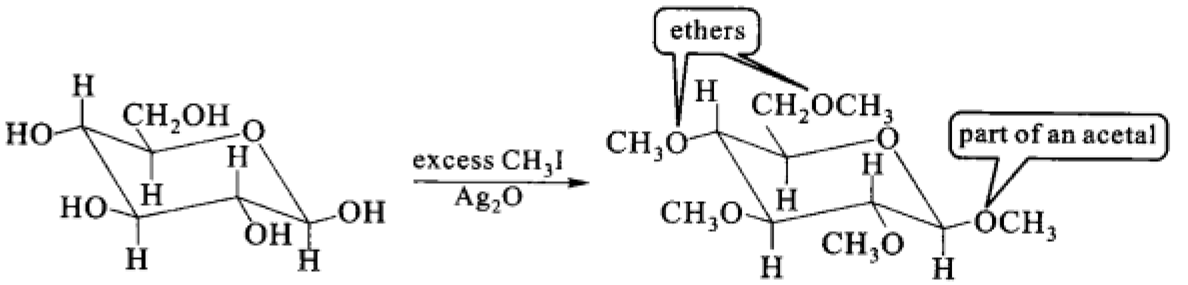
Aldose **E** is optically active, but treatment with sodium borohydride converts it to an optically inactive alditol. Ruff degradation

of **E** gives **F**, whose alditol is optically inactive. Ruff degradation of **F** gives optically active D-glyceraldehyde. Give the structures and names of **E** and **F** and their optically inactive alditols.

24–17 Determination of Ring Size; Periodic Acid Cleavage of Sugars

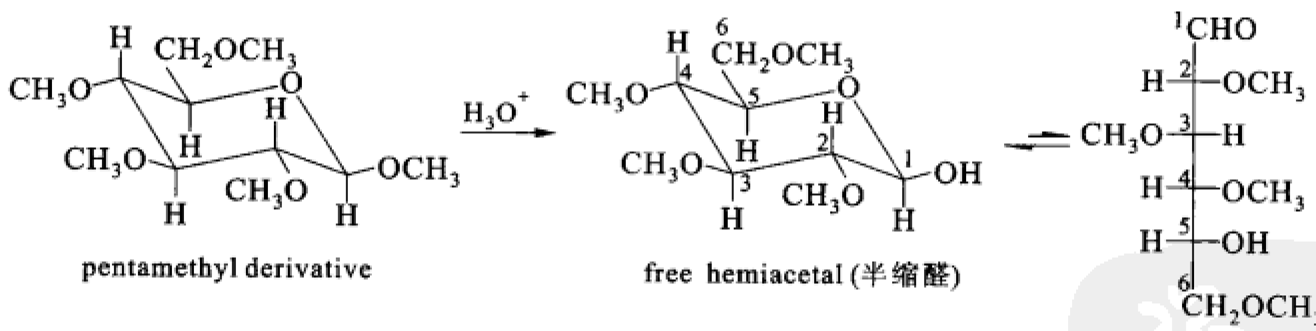
Using methods similar to Fischer's, the straight-chain form of any monosaccharide can be worked out. As we have seen, however, monosaccharides exist mostly as cyclic pyranose or furanose hemiacetals. These hemiacetals are in equilibrium with the openchain forms, so sugars can react like hemiacetals or like ketones and aldehydes. How can we freeze this equilibrium and determine the optimum ring size for any given sugar? Sir Walter Haworth (inventor of the Haworth projection) used some simple chemistry to determine the pyranose structure of glucose in 1926.

Glucose is converted to a pentamethyl derivative by treatment with methyl iodide and silver oxide. The five methyl groups are not the same, however. Four are methyl ethers, but one is the glycosidic methyl group of an acetal.



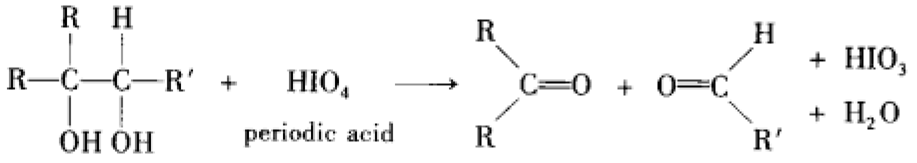
β-D-glucose (β–D–葡萄糖) methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucoside (2,3,4,6–四–*O*–甲基–β–D–甲基葡萄糖苷)

Acetals are easily hydrolyzed by dilute acid, but ethers are stable under these conditions. Treatment of the pentamethyl glucose derivative with dilute acid hydrolyzes only the acetal methyl group. Haworth determined that the free hydroxyl group is on C5 of the hydrolyzed ether, showing that the cyclic form of glucose is a pyranose.



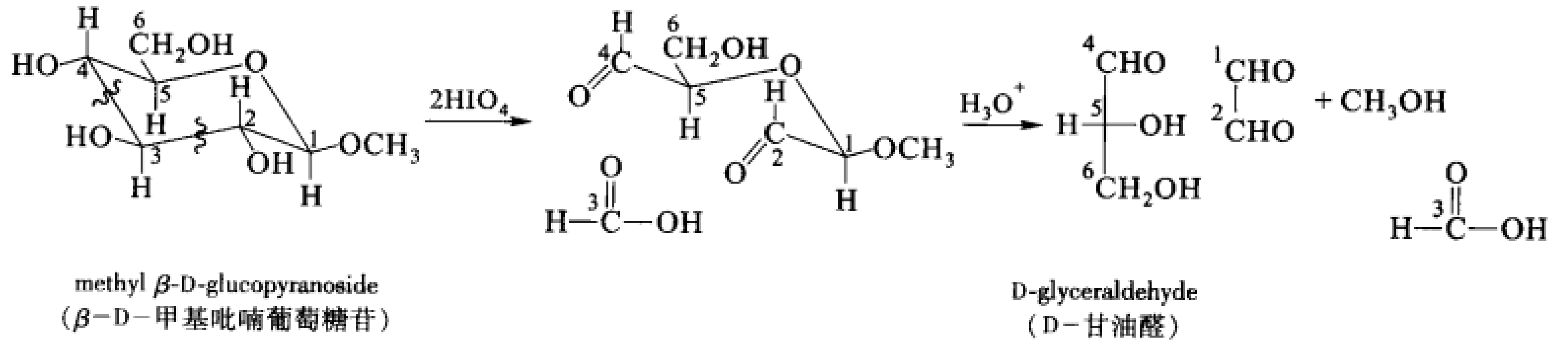
pentamethyl derivative free hemiacetal (半缩醛) open-chain form 2,3,4,6-*O*-tetramethyl-D-glucose (2,3,4,6–四–*O*–甲基–D–葡萄糖)

Periodic Acid Cleavage of Carbohydrates Another method used to determine the size of carbohydrate rings is cleavage by periodic acid. Recall that periodic acid cleaves vicinal diols to give two carbonyl compounds, either ketones or aldehydes, depending on the substitution of the reactant.



vicinal diol (连二醇) ketones and aldehydes

Because ether and acetal groups are not affected, periodic acid cleavage of a glycoside can help to determine the size of the ring. For example, periodic acid oxidation of methyl β-D-glucopyranoside gives the following products. The structure of the fragment containing C4, C5, and C6 implies that the original glycoside was a six-membered ring bonded through the C5 oxygen atom.



PROBLEM 24−17

(a) Draw the reaction of methyl β-D-fructofuranoside with periodic acid, and predict the products.

(b) Draw the structure of a hypothetical methyl β-D-fructopyranoside, and predict the products from periodic acid oxidation.

(c) The reaction of methyl β-D-glucopyranoside with periodic acid (shown above) gives only the D-(+) enantiomer of glyceraldehyde (among other products). If you oxidized an aldohexose glycoside with periodic acid and one of the products was the L-(−) enantiomer of glyceraldehyde, what would that tell you about the sugar?

24−18 Disaccharides

As we have seen, the anomeric carbon of a sugar can react with the hydroxyl group of an alcohol to give an acetal called a *glycoside*. If the hydroxyl group is part of another sugar molecule, then the glycoside product is a **disaccharide**, a sugar composed of two monosaccharide units (Figure 24−12).

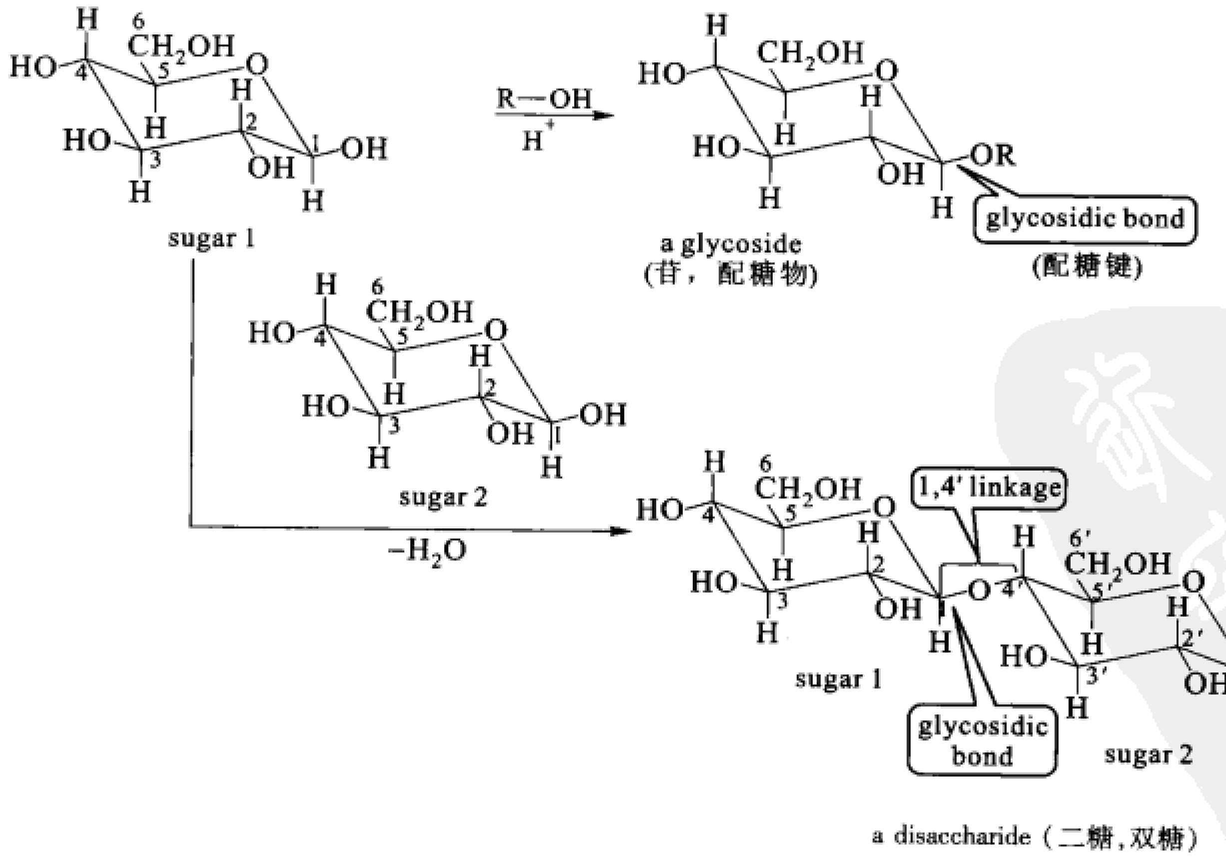


Figure 24−12 Disaccharides. A sugar reacts with an alcohol to give an acetal called a glycoside. When the alcohol is part of another sugar, the product is a disaccharide.

In principle, the anomeric carbon can react with *any* of the hydroxyl groups of another sugar to form a disaccharide. In naturally occurring disaccharides, however, there are three common glycosidic bonding arrangements.

1. A 1,4′ link. The anomeric carbon is bonded to the oxygen atom on C4 of the second sugar. The prime symbol (′) in 1,4′indicates that C4 is on the second sugar.

2. A 1,6′ link. The anomeric carbon is bonded to the oxygen atom on C6 of the second sugar.

3. A 1,1′ link. The anomeric carbon of the first sugar is bonded through an oxygen atom to the anomeric carbon of the second sugar.

We will consider some naturally occurring disaccharides with these common glycosidic linkages.

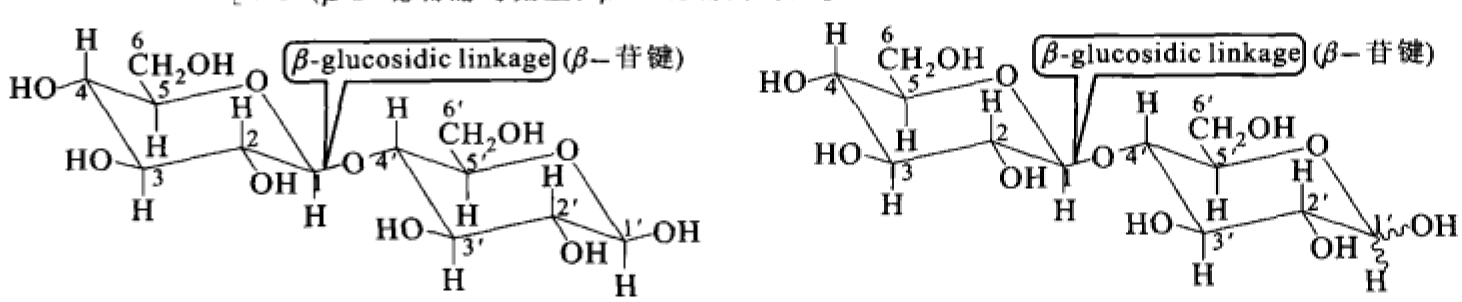
24–18A The 1,4′ Linkage: Cellobiose, Maltose, and Lactose

The most common glycosidic linkage is the 1,4′ link. The anomeric carbon of one sugar is bonded to the oxygen atom on C4 of the second ring.

Cellobiose: A β-1,4′ Glucosidic Linkage *Cellobiose*, the disaccharide obtained by partial hydrolysis of cellulose, contains a 1,4′ linkage. In cellobiose, the anomeric carbon of one glucose unit is linked through an equatorial (β) carbon-oxygen bond to C4 of another glucose unit. This β-1,4′ linkage from a *glucose* acetal is called a β-1,4′ ***gluco*sidic linkage**.

Cellobiose, 4-O-(β-D-glucopyranosyl)-β-D-glucopyranose or 4-O-(β-D-glucopyranosyl)-D-glucopyranose

[4-O-(β-D-吡喃葡萄糖基)-β-D-吡喃葡萄糖]



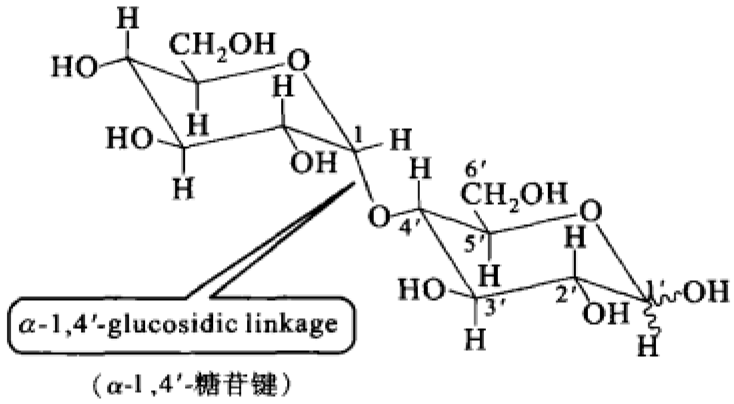
Two alternative ways of drawing and naming cellobiose

The complete name for cellobiose, 4-O-(β-D-glucopyranosyl)-β-D-glucopyranose, gives its structure. This name says that a β-D-glucopyranose ring (the right-hand ring) is substituted in its 4-position by an oxygen attached to a (β-D-glucopyranosyl) ring, drawn on the left. The name in parentheses says the substituent is a β-glucose, and the *-syl* ending indicates that this ring is a glycoside. The left ring with the *-syl* ending is an acetal and cannot mutarotate, while the right ring with the *-ose* ending is a hemiacetal and can mutarotate. Because cellobiose has a glucose unit in the hemiacetal form (and therefore is in equilibrium with its open-chain aldehyde form), it is a reducing sugar. Once again, the *-ose* ending indicates a mutarotating, reducing sugar.

Mutarotating sugars are often shown with a wavy line to the free anomeric hydroxyl group, signifying that they can exist as an equilibrium mixture of the two anomers. Their names are often given without specifying the stereochemistry of this mutarotating hydroxyl group, as in 4-O-(β-D-glucopyranosyl)-D-glucopyranose.

Maltose: An α-1,4′-Glucosidic Linkage *Maltose* is a disaccharide formed when starch is treated with sprouted barley, called *malt*. This malting process is the first step in brewing beer, converting polysaccharides to disaccharides and monosaccharides that ferment more easily. Like cellobiose, maltose contains a 1,4′-glycosidic linkage between two glucose units. The difference in maltose is that the stereochemistry of the glucosidic linkage is α rather than β.

Maltose, 4-O-(α-D-glucopyranosyl)-D-glucopyranose [4-O-(α-D-吡喃葡萄糖基)-D-吡喃葡萄糖]



Like cellobiose, maltose has a free hemiacetal ring (on the right). This hemiacetal is in equilibrium with its open-chain form, and it mutarotates and can exist in either the α or β anomeric form. Because maltose exists in equilibrium with an open-chain aldehyde, it reduces Tollens reagent, and maltose is a reducing sugar.

PROBLEM 24-18

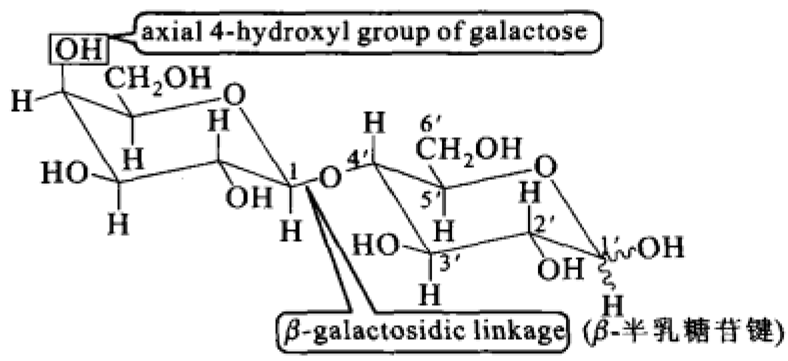
Draw the structure of the individual mutarotating α and β anomers of maltose.

PROBLEM 24-19

Give an equation to show the reduction of Tollens reagent by maltose.

Lactose: A β-1,4′ Galactosidic Linkage *Lactose* is similar to cellobiose, except that the glycoside (the left ring) in lactose is galactose rather than glucose. Lactose is composed of one galactose unit and one glucose unit. The two rings are linked by a β-glycosidic bond of the galactose acetal to the 4-position on the glucose ring: a β-1,4′ ***galacto*sidic linkage**.

Lactose, 4-O-(β-D-galactopyranosyl)-D-glucopyranose [4-*O*-(β-D-吡喃半乳糖基)-D-吡喃葡萄糖]



Lactose occurs naturally in the milk of mammals, including cows and humans. Hydrolysis of lactose requires a β-galactosidase enzyme (sometimes called lactase). Some humans synthesize a β-galactosidase, but others do not. This enzyme is present in the digestive fluids of normal infants to hydrolyze their mother's milk. Once the child stops drinking milk, production of the enzyme gradually stops. In most parts of the world, people do not use milk products after early childhood, and the adult population can no longer digest lactose. Consumption of milk or milk products can cause digestive discomfort in *lactose-intolerant* people who lack the β-galactosidase enzyme. Lactose-intolerant infants must drink soybean milk or another lactose-free formula.

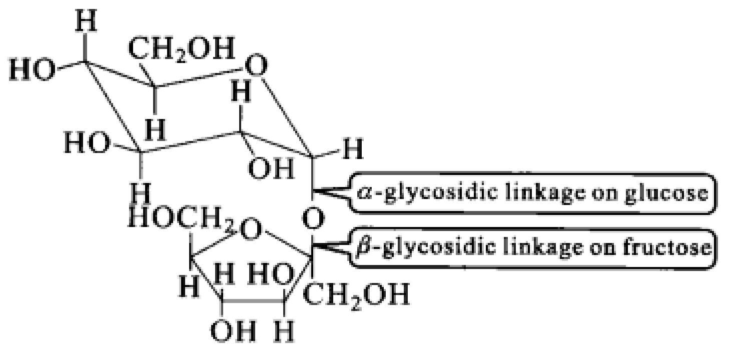
PROBLEM 24-20

Does lactose mutarotate? Is it a reducing sugar? Explain. Draw the two anomeric forms of lactose.

24-18B Linkage of Two Anomeric Carbons: Sucrose

Some sugars are joined by a direct glycosidic linkage between their anomeric carbon atoms: a 1,1′ linkage. *Sucrose* (common table sugar), for example, is composed of one glucose unit and one fructose unit bonded by an oxygen atom linking their anomeric carbon atoms. (Because fructose is a ketose and its anomeric carbon is C2, this is actually a 1,2′ linkage.) Notice that the linkage is in the α position with respect to the glucose ring and in the β position with respect to the fructose ring.

Sucrose, α-D-glucopyranosyl-β-D-fructofuranoside (α-D-吡喃葡萄糖基-β-D-呋喃果糖苷)
(*or β-D-fructofuranosyl-α-D-glucopyranoside*) (β-D-呋喃果糖基-α-D-吡喃葡萄糖苷)



Both monosaccharide units in sucrose are present as acetals, or glycosides. Neither ring is in equilibrium with its open-chain aldehyde or ketone form, so sucrose does not reduce Tollens reagent and it cannot mutarotate. Because both units are glycosides, the systematic name for sucrose can list either of the two glycosides as being a substituent on the other. Both systematic names end in the *-oside* suffix, indicating a nonmutarotating, nonreducing sugar. Like many other common names, *sucrose* ends in the *-ose* ending even though it is a nonreducing sugar. Common names are not reliable indicators of the properties of sugars.

Sucrose is hydrolyzed by enzymes called *invertases*, found in honeybees and yeasts, that specifically hydrolyze the β-D-fructofuranoside linkage. The resulting mixture of glucose and fructose is called *invert sugar* because hydrolysis converts the positive rotation [+66.5°] of sucrose to a negative rotation that is the average of glucose [+52.7°] and fructose [−92.4°]. The most common form of invert sugar is honey, a supersaturated mixture of glucose and fructose hydrolyzed from sucrose by the invertase enzyme of honeybees. Glucose and fructose were once called *dextrose* and *levulose*, respectively, according to their opposite signs of rotation.

PROBLEM 24-21

Trehalose is a nonreducing disaccharide ($C_{12}H_{22}O_{11}$) isolated from the poisonous mushroom *Amanita muscaria*. Treatment with an α-glucosidase converts trehalose to two molecules of glucose, but no reaction occurs when trehalose is treated with a β-glucosidase. When trehalose is methylated by dimethyl sulfate in mild base and then hydrolyzed, the only product is 2,3,4,6-tetra-*O*-methylglucose. Propose a complete structure and systematic name for trehalose.

24-19 Polysaccharides

Polysaccharides are carbohydrates that contain many monosaccharide units joined by glycosidic bonds. They are one class of *biopolymers*, or naturally occurring polymers. Smaller polysaccharides, containing about three to ten monosaccharide units, are sometimes called **oligosaccharides**. Most polysaccharides have hundreds or thousands

of simple sugar units linked together into long polymer chains. Except for units at the ends of chains, all the anomeric carbon atoms of polysaccharides are involved in acetal glycosidic links. Therefore, polysaccharides give no noticeable reaction with Tollens reagent, and they do not mutarotate.

24－19A Cellulose

Cellulose, a polymer of D-glucose, is the most abundant organic material. Cellulose is synthesized by plants as a structural material to support the weight of the plant. Long cellulose molecules, called *microfibrils*, are held in bundles by hydrogen bonding between the many —OH groups of the glucose rings. About 50% of dry wood and about 90% of cotton fiber is cellulose.

Cellulose is composed of D-glucose units linked by β-1,4′ glycosidic bonds. This bonding arrangement (like that in cellobiose) is rather rigid and very stable, giving cellulose desirable properties for a structural material. Figure 24－13 shows a partial structure of cellulose.

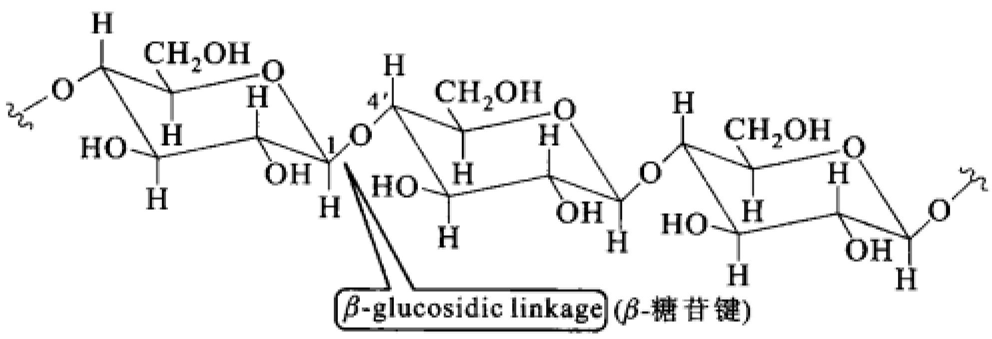


Figure 24－13 Partial structure of cellulose.

Humans and other mammals lack the β-glucosidase enzyme needed to hydrolyze cellulose, so they cannot use it directly for food. Several groups of bacteria and protozoa can hydrolyze cellulose, however. Termites and ruminants maintain colonies of these bacteria in their digestive tracts. When a cow eats hay, these bacteria convert about 20% to 30% of the cellulose to digestible carbohydrates.

24－19B Starches: Amylose, Amylopectin, and Glycogen

Plants use starch granules for storing energy. When the granules are dried and ground up, different types of starches can be separated by mixing them with hot water. About 20% of the starch is water-soluble *amylose*, and the remaining 80% is water-insoluble *amylopectin*. When starch is treated with dilute acid or appropriate enzymes, it is progressively hydrolyzed to maltose and then to glucose.

Amylose Like cellulose, **amylose** is a linear polymer of glucose with 1,4′ glycosidic linkages. The difference is in the stereochemistry of the linkage. Amylose has α-1,4′ links, while cellulose has β-1,4′ links. A partial structure of amylose is shown in Figure 24－14.

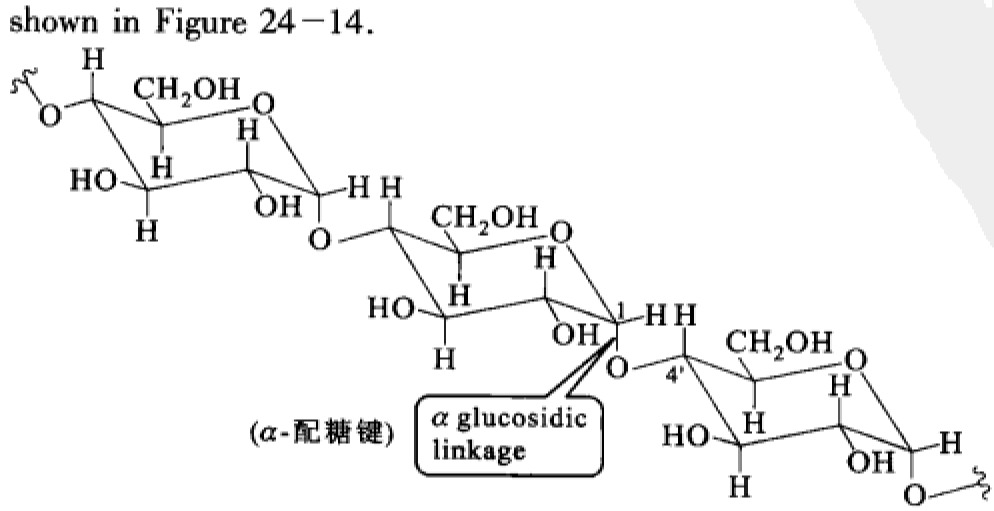


Figure 24－14 Partial structure of amylose (直链淀粉).

The subtle stereochemical difference between cellulose and amylose results in some striking physical and chemical differences. The α linkage in amylose kinks the polymer chain into a helical structure. This kinking increases hydrogen bonding with water and lends additional solubility. As a result, amylose is soluble in water, and cellulose is not. Cellulose is stiff and sturdy, but amylose is not. Unlike cellulose, amylose is an excellent food source. The α-1,4′ glucosidic linkage is easily hydrolyzed by an α-glucosidase enzyme, present in all animals.

The helical structure of amylose also serves as the basis for an interesting and useful reaction. The inside of the helix is just the right size and polarity to accept an iodine (I_2) molecule. When iodine is lodged within this helix, a deep blue starch-iodine complex results. This is the basis of the *starch-iodide* test for oxidizers. The material to be tested is added to an aqueous solution of amylose and potassium iodide. If the material is an oxidizer, some of the iodide (I^-) is oxidized to iodine (I_2), which forms the blue complex with amylose.

Amylopectin, the insoluble fraction of starch, is also primarily an α-1,4′ polymer of glucose. The difference between amylose and amylopectin lies in the branched nature of amylopectin, with a branch point about every 20 to 30 glucose units. Another chain starts at each branch point, connected to the main chain by an α-1,6′ glycosidic linkage. A partial structure of amylopectin, including one branch point, is shown in Figure 24-15.

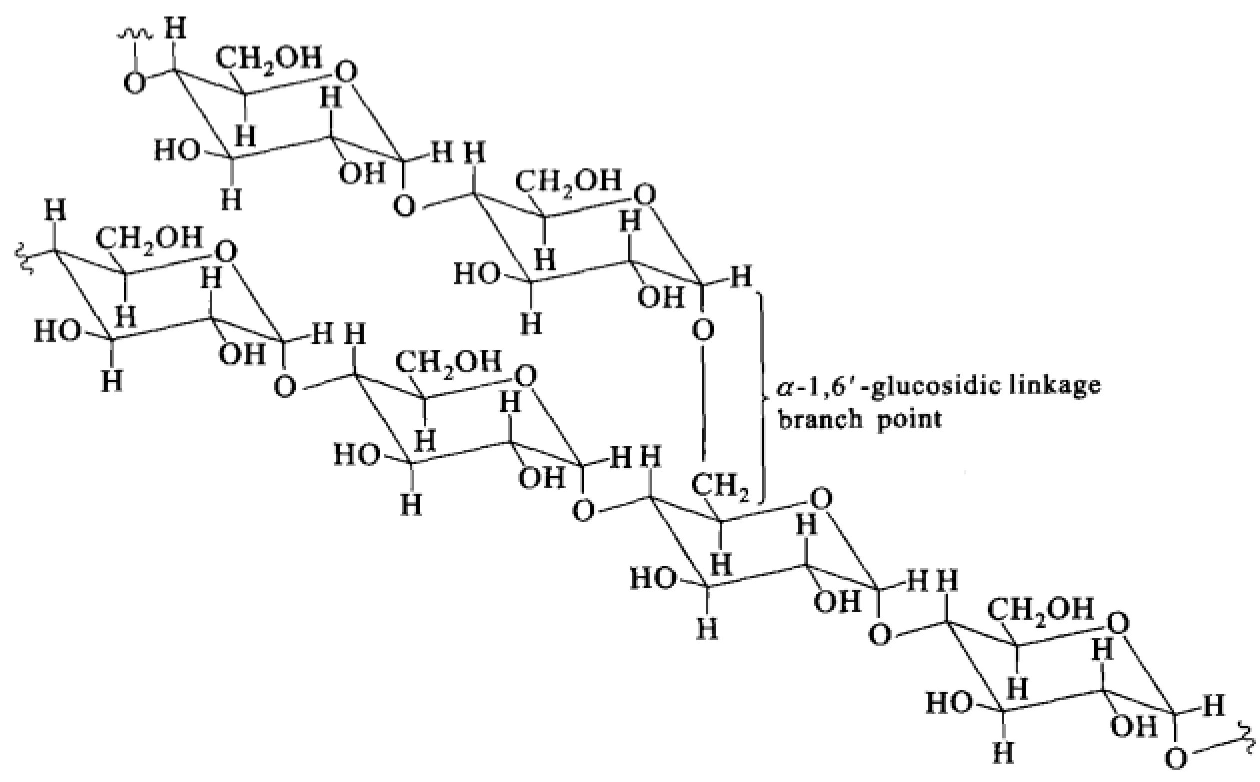


Figure 24-15 Partial structure of amylopectin (支链淀粉). Glycogen (糖原,动物淀粉) has a similar structure, except that its branching is more extensive.

Glycogen is the carbohydrate that animals use to store glucose for readily available energy. A large amount of glycogen is stored in the muscles themselves, ready for immediate hydrolysis and metabolism. Additional glycogen is stored in the liver, where it can be hydrolyzed to glucose for secretion into the bloodstream, providing an athlete with a "second wind."

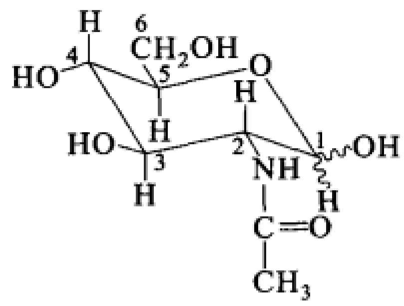
The structure of glycogen is similar to that of amylopectin, but with more extensive branching. The highly branched structure of glycogen leaves many end groups available for quick hydrolysis to provide glucose needed for metabolism.

24-19C Chitin: A Polymer of *N*-Acetylglucosamine

Chitin (pronounced *kī′-t′n*, rhymes with Titan) forms the exoskeletons of insects. In crustaceans, chitin forms a

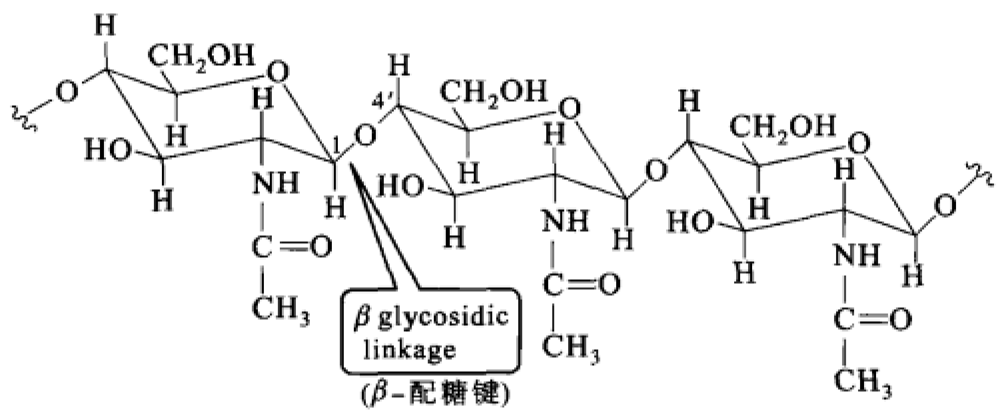
matrix that binds calcium carbonate crystals into the exoskeleton. Chitin is different from the other carbohydrates we have studied. It is a polymer of *N*-acetylglucosamine, an **amino sugar** (actually an amide) that is common in living organisms. In *N*-acetylglucosamine, the hydroxyl group on C2 of glucose is replaced by an amino group (forming glucosamine), and that amino group is acetylated.

N-Acetylglucosamine, or 2-acetamido-2-deoxy-D-glucose (2-乙酰氨基-2-脱氧-D-葡萄糖,*N*-乙酰基葡糖胺)



Chitin is bonded like cellulose, except using *N*-acetylglucosamine instead of glucose. Like other amides, *N*-acetylglucosamine forms exceptionally strong hydrogen bonds between the amide carbonyl groups and N—H protons. The glycosidic bonds are β-1,4′ links, giving chitin structural rigidity, strength, and stability that exceed even that of cellulose. Unfortunately, this strong, rigid polymer cannot easily expand, so it must be shed periodically by molting as the animal grows.

Chitin (甲壳素), *or poly (1,4′-O-β-2-acetamido-2-deoxy-D-glucopyranoside)*, [2-乙酰氨基-2-脱氧-β-(1,4′)-D-葡聚糖]
a β-1,4-linked polymer of N-acetylglucosamine



24-20 Nucleic Acids: Introduction

Nucleic acids are substituted polymers of the aldopentose ribose that carry an organism's genetic information. A tiny amount of DNA in a fertilized egg cell determines the physical characteristics of the fully developed animal. The difference between a frog and a human being is encoded in a relatively small part of this DNA. Each cell carries a complete set of genetic instructions that determine the type of cell, what its function will be, when it will grow and divide, and how it will synthesize all the proteins, enzymes, carbohydrates, and other substances the cell and the organism need to survive.

The two major classes of nucleic acids are **ribonucleic acids (RNA)** and **deoxyribonucleic acids (DNA)**. In a typical cell, DNA is found primarily in the nucleus, where it carries the permanent genetic code. The molecules of DNA are huge, with molecular weights up to 50 billion. When the cell divides, DNA replicates to form two copies for the daughter cells. DNA is relatively stable, providing a medium for transmission of genetic information from one generation to the next.

RNA molecules are typically much smaller than DNA, and they are more easily hydrolyzed and broken

down. RNA commonly serves as a working copy of the nuclear DNA being decoded. Nuclear DNA directs the synthesis of *messenger RNA*, which leaves the nucleus to serve as a template for the construction of protein molecules in the ribosomes. The messenger RNA is then enzymatically cleaved to its component parts, which become available for assembly into new RNA molecules to direct other syntheses.

The backbone of a nucleic acid is a polymer of ribofuranoside rings (five-membered rings of the sugar ribose) linked by phosphate ester groups. Each ribose unit carries a heterocyclic *base* that provides part of the information needed to specify a particular amino acid in protein synthesis. Figure 24–16 shows the ribose-phosphate backbone of RNA.

DNA and RNA each contain four monomers, called **nucleotides**, that differ in the structure of the bases bonded to the ribose units. Yet this deceptively simple structure encodes complex information just as the 0 and 1 bits used by a computer encode complex programs. First we consider the structure of individual nucleotides, then the bonding of these monomers into single-stranded nucleic acids, and finally the base pairing that binds two strands into the double helix of nuclear DNA.

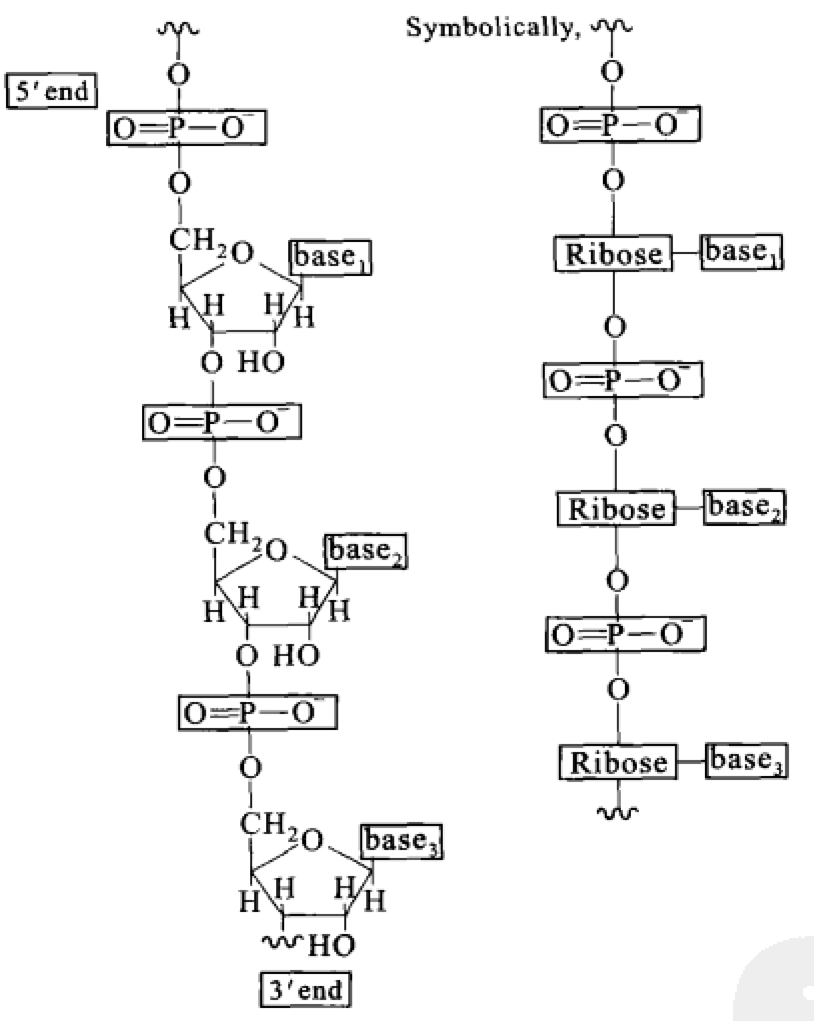
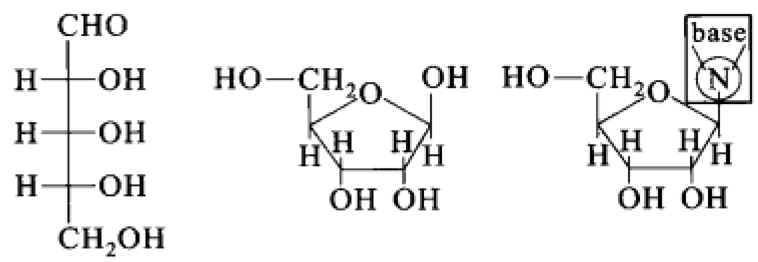


Figure 24–16 A short segment of the RNA (核糖核酸) polymer.

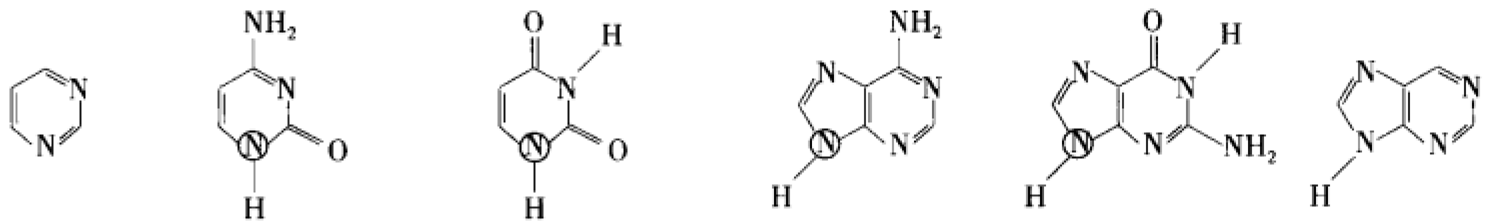
24–21 Ribonucleosides and Ribonucleotides

Ribonucleosides are components of RNA based on glycosides of the furanose form of D-ribose. We have seen that a glycoside may have an aglycone (the substituent on the anomeric carbon) bonded by a nitrogen atom. A ribonucleoside is a β-D-ribofuranoside (a β-glucosidase of D-ribofuranoside) whose aglycone is a heterocyclic nitrogen base. The following structures show the open-chain and furanose forms of ribose, and a ribonucleoside with a generic base bonded through a nitrogen atom.



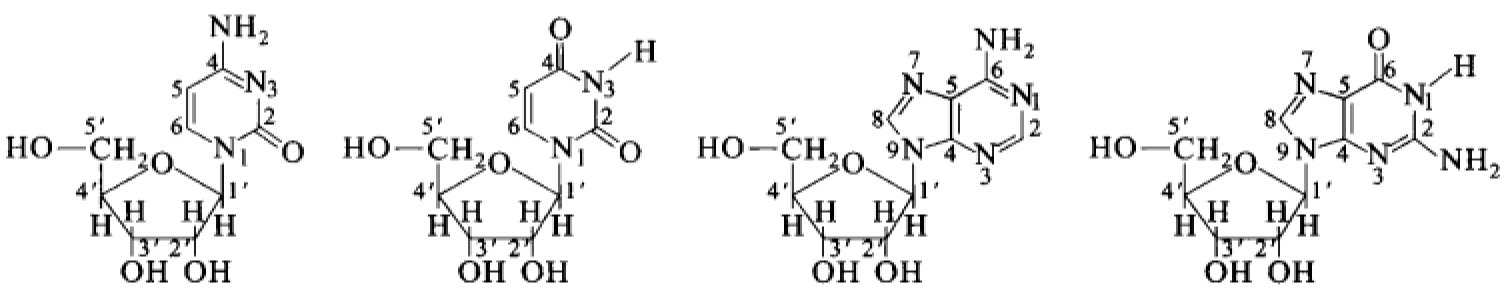
D-ribose（D-核糖）　β-D-ribofuranose（β-D-呋喃核糖）　a ribonucleoside（核糖核苷）

The four bases commonly found in RNA are divided into two classes: The monocyclic compounds cytosine and uracil are called *pyrimidine bases* because they resemble substituted pyrimidines, and the bicyclic compounds adenine and guanine are called *purine bases* because they resemble the bicyclic heterocycle purine.



pyrimidine（嘧啶）　cytosine（C）（胞嘧啶）　uracil（U）（尿嘧啶）　pyrimidine bases　adenine（A）（腺嘌呤）　guanine（G）（鸟嘌呤）　purine bases　purine（嘌呤）

When bonded to ribose through the circled nitrogen atoms, the four heterocyclic bases make up the four ribonucleosides cytidine, uridine, adenosine, and guanosine (Figure 24-17). Notice that the two ring systems (the base and the sugar) are numbered separately, and the carbons of the sugar are given primed numbers. For example, the 3′ carbon of cytidine is C3 of the ribose ring.

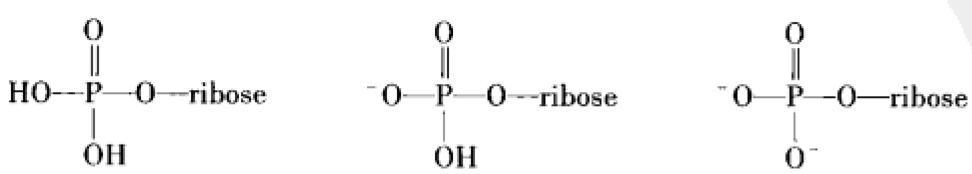


cytidine（C）（胞嘧啶核苷）　uridine（U）（尿嘧啶核苷）　adenosine（A）（腺嘌呤核苷）　guanosine（G）（鸟嘌呤核苷）

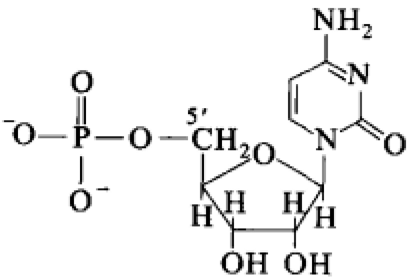
Figure 24-17 The four common ribonucleosides are cytidine, uridine, adenosine, and guanosine.

Ribonucleotides Ribonucleic acid consists of ribonucleosides bonded together into a polymer. This polymer cannot be bonded by glycosidic linkages like those of other polysaccharides because the glycosidic bonds are already used to attach the heterocyclic bases. Instead, the ribonucleoside units are linked by phosphate esters. The 5′-hydroxyl group of each ribofuranoside is esterified to phosphoric acid. A ribonucleoside that is phosphorylated at its 5′ carbon is called a **ribonucleotide** ("tied" to phosphate). The four common ribonucleotides, shown in Figure 24-18, are simply phosphorylated versions of the four common ribonucleosides.

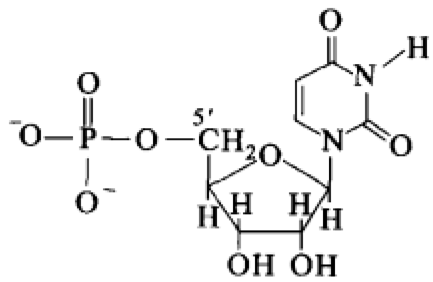
The phosphate groups of these ribonucleotides can exist in any of three ionization states, depending on the pH of the solution. At the nearly neutral pH of most organisms (pH = 7.4), there is one proton on the phosphate group. By convention, however, these groups are usually written completely ionized.



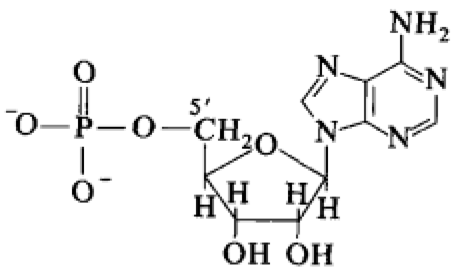
in acid　nearly neutral　in base (usually written)



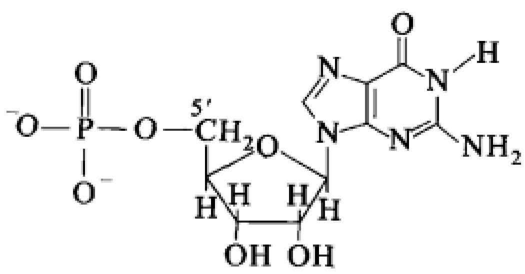
(胞苷一磷酸)
cytidine monophosphate,
CMP(cytidylic acid)
(胞苷酸)



(尿苷一磷酸)
uridine monophosphate,
UMP(uridylic acid)
(尿苷酸)



(腺苷一磷酸)
adenosine monophosphate,
AMP(adenylic acid)
(腺苷酸)



(鸟苷一磷酸)
guanosine monophosphate,
GMP(guanidylic acid)
(鸟苷酸)

Figure 24−18 Four common ribonucleotides (核糖核苷酸). These are ribonucleosides (核糖核苷) esterified by phosphoric acid at their 5′-position, the $—CH_2OH$ at the end of the ribose chain.

24−22 The Structure of Ribonucleic Acid

Now that we recognize the individual ribonucleotides, we can consider how these units are bonded into the RNA polymer. Each nucleotide has a phosphate group on its 5′ carbon (the end carbon of ribose) and a hydroxyl group on the 3′ carbon. Two nucleotides are joined by a phosphate ester linkage between the 5′-phosphate group of one nucleotide and the 3′-phosphate group of another (Figure 24−19).

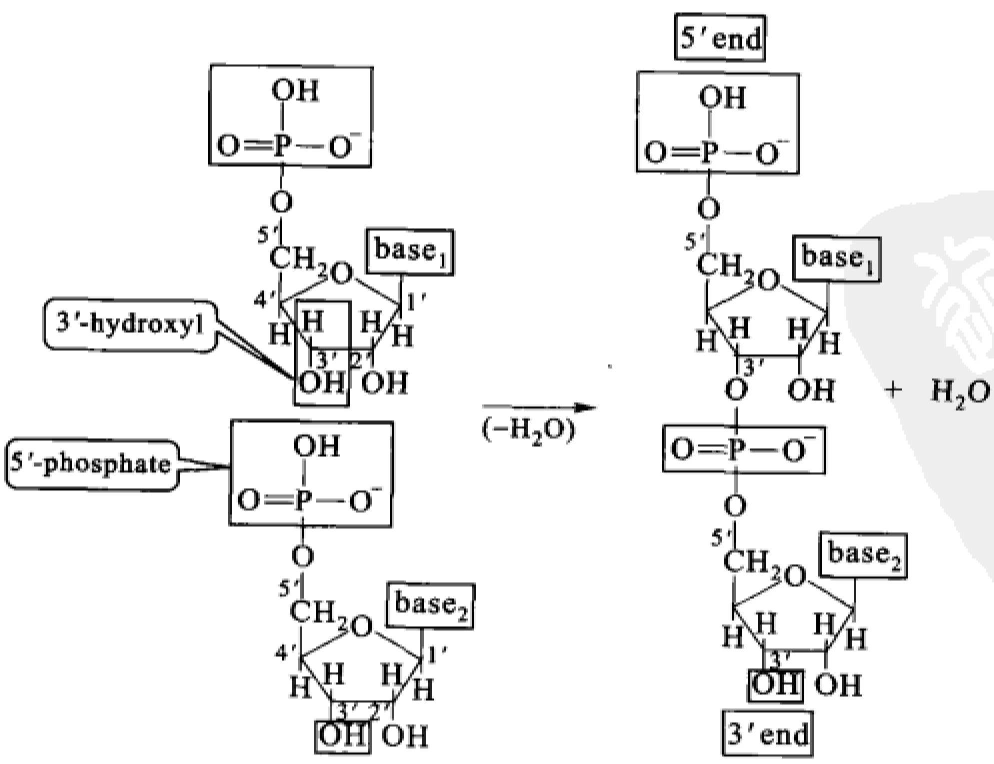
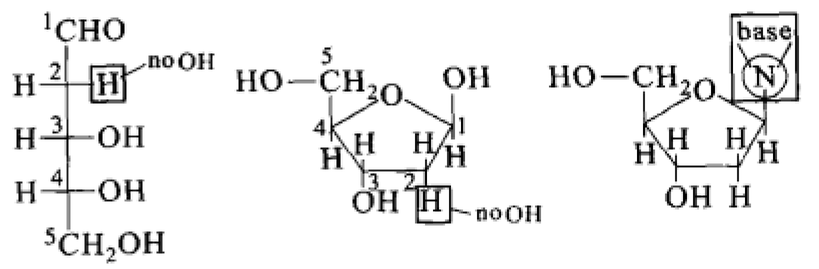


Figure 24−19 Phosphate linkage of nucleotides (核苷酸) in RNA.

The RNA polymer consists of many nucleotide units bonded this way, with a phosphate ester linking the 5′ end of one nucleoside to the 3′ end of another. A molecule of RNA always has two ends (unless it is in the form of a large ring). One end has a free 3′ group, and the other end has a free 5′ group. We refer to the ends as the 3′ *end* and the 5′ *end*, and we refer to directions of replication as the *3′→5′ direction* and the *5′→3′ direction*. Figures 24-16 and 24-19 show short segments of RNA with the 3′ end and the 5′ end labeled.

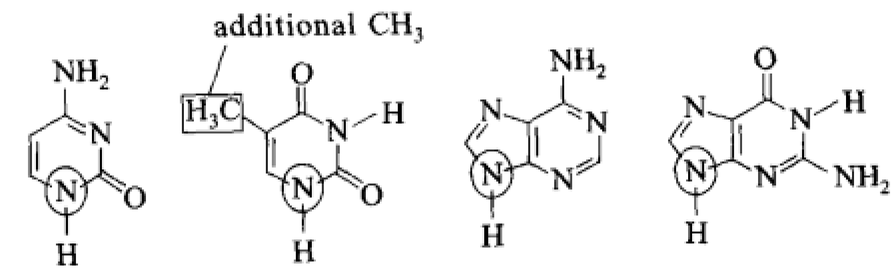
24-23 Deoxyribose and the Structure of Deoxyribonucleic Acid

All our descriptions of ribonucleosides, ribonucleotides, and ribonucleic acid also apply to the components of DNA. The principal difference between RNA and DNA is the presence of D-2-deoxyribose as the sugar in DNA instead of the D-ribose found in RNA. The prefix *deoxy*-means that an oxygen atom is missing, and the number 2 means it is missing from C2.



D-2-deoxyribose (D-2-脱氧核糖) | β-D-2-deoxyribofuranose (β-D-2-呋喃脱氧核糖) | a deoxyribonucleoside (脱氧核糖核苷)

Another key difference between RNA and DNA is the presence of thymine in DNA instead of the uracil in RNA. Thymine is simply uracil with an additional methyl group. The four common bases of DNA are cytosine, thymine, adenine, and guanine.

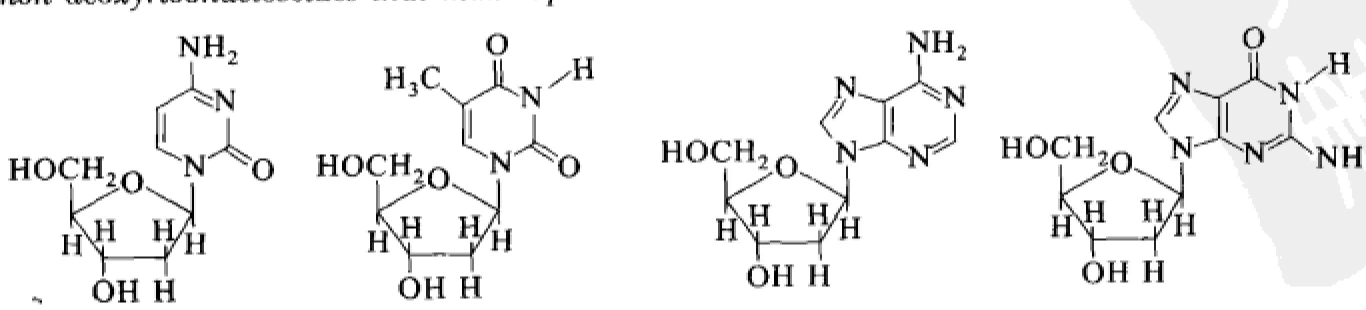


cytosine (C) (胞嘧啶) | thymine (T) (胸腺嘧啶) | adenine (A) (腺嘌呤) | guanine (G) (鸟嘌呤)

pyrimidine bases | purine bases

These four bases are incorporated into deoxyribonucleosides and deoxyribonucleotides similar to the bases in ribonucleosides and ribonucleotides. The following structures show the common nucleosides that make up DNA. The corresponding nucleotides are simply the same structures with phosphate groups at the 5′ positions.

Four common deoxyribonucleosides that make up DNA



deoxycytidine (胞嘧啶脱氧核苷) | deoxythymidine (胸腺嘧啶脱氧核苷) | deoxyadenosine (腺嘌呤脱氧核苷) | deoxyguanosine (鸟嘌呤脱氧核苷)

The structure of the DNA polymer is similar to that of RNA, except there are no hydroxyl groups on the 2′ carbon atoms of the ribose rings. The alternating deoxyribose rings and phosphates act as the backbone, while the bases attached to the deoxyribose units carry the genetic information. The sequence of nucleotides is called the **primary structure** of the DNA strand.

24-23A Base Pairing

Having discussed the primary structure of DNA and RNA, we now consider how the nucleotide sequence is reproduced or transcribed into another molecule. This information transfer takes place by an interesting hydrogen-bonding interaction between specific pairs of bases.

Each pyrimidine base forms a stable hydrogen-bonded pair with only one of the two purine bases (Figure 24-20). Cytosine forms a base pair, joined by three hydrogen bonds, with guanine. Thymine (or uracil in RNA) forms abase pair with adenine, joined by two hydrogen bonds. Guanine is said to be *complementary* to cytosine, and adenine is complementary to thymine. This base pairing was first suspected in 1950, when Erwin Chargaff of Columbia University noticed that various DNAs, taken from a wide variety of species, had about equal amounts of adenine and thymine and about equal amounts of guanine and cytosine.

Figure 24-20 Base pairing in DNA and RNA.

24-23B The Double Helix of DNA

In 1953, James D. Watson and Francis C. Crick used X-ray diffraction patterns of DNA fibers to determine the molecular structure and conformation of DNA. They found that DNA contains two complementary polynucleotide chains held together by hydrogen bonds between the paired bases. Figure 24-21 shows a portion of the double strand of DNA, with each base paired with its complement. The two strands are *antiparallel*: One strand is arranged 3′→5′ from left to right, while the other runs in the opposite direction, 5′→3′ from left to right.

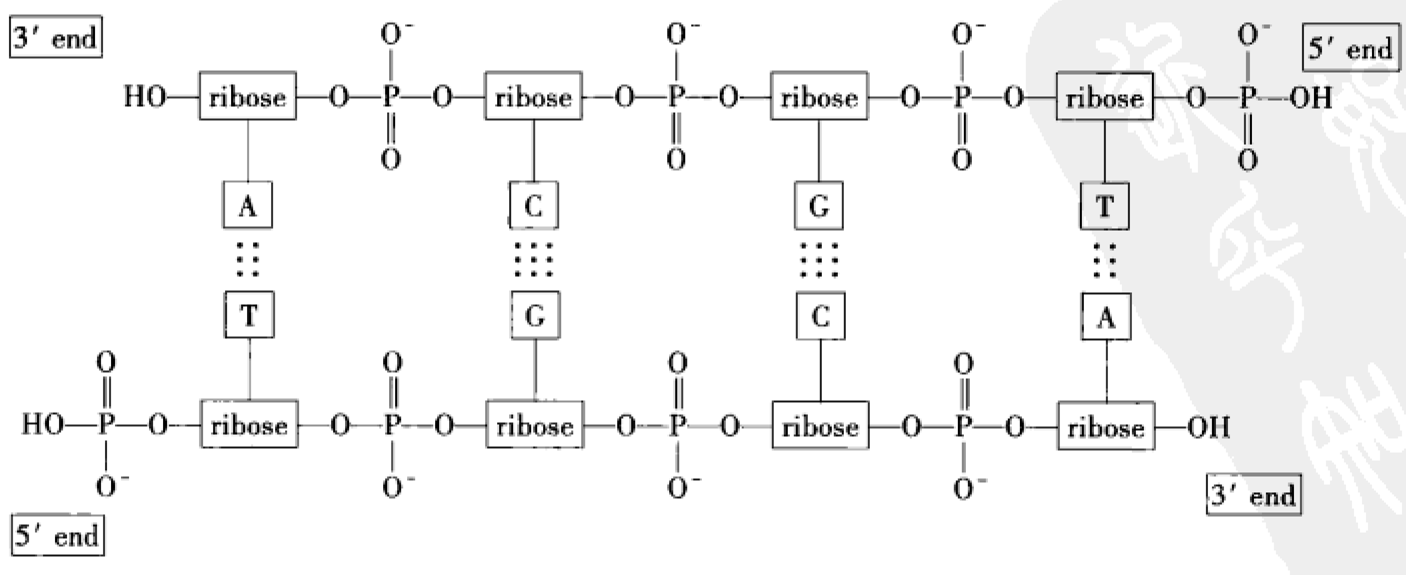


Figure 24-21 Antiparallel strands of DNA.

Watson and Crick also found that the two complementary strands of DNA are coiled into a helical conformation about 20 Å in diameter, with both chains coiled around the same axis. The helix makes a complete turn for every ten residues, or about one turn in every 34 Å of length. Figure 24-22 shows the double helix of DNA. In this drawing, the two sugar-phosphate backbones form the vertical double helix with the heterocyclic bases stacked horizontally in the center. Attractive stacking forces between the pi clouds of the aromatic pyrimidine and purine bases are substantial, further helping to stabilize the helical arrangement.

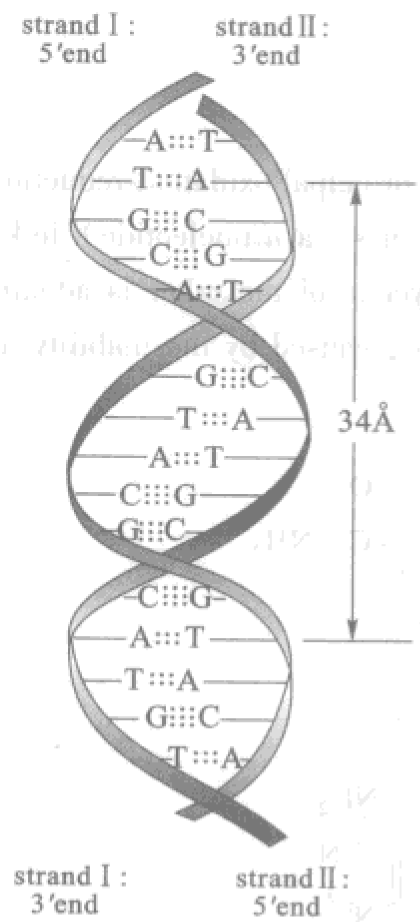


Figure 24-22 Double helix (双螺旋) of DNA.

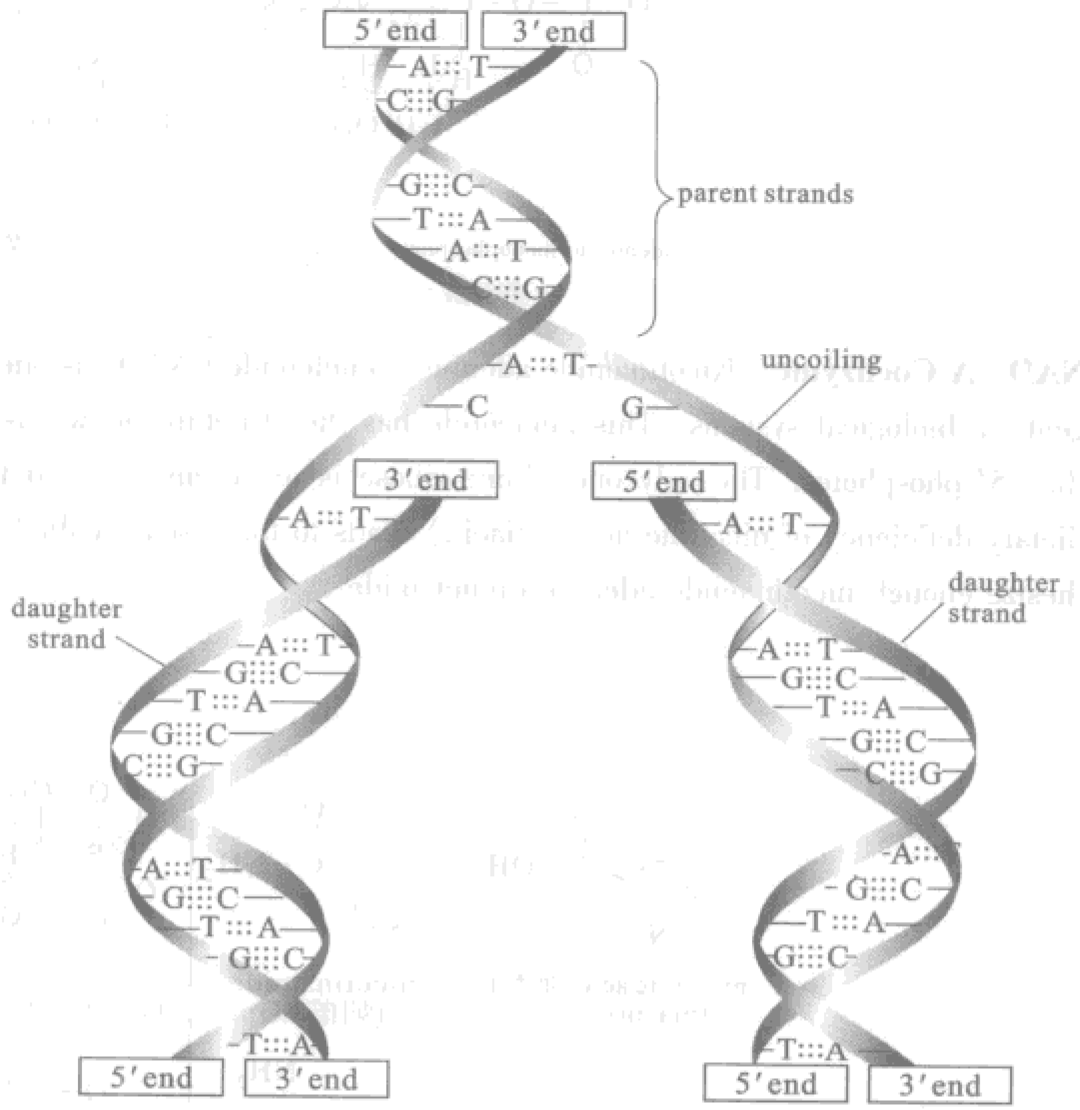


Figure 24-23 Replication of the double strand of DNA.

When DNA undergoes replication (in preparation for cell division), an enzyme uncoils part of the double strand. Individual nucleotides naturally hydrogen bond to their complements on the uncoiled part of the original strand, and a *DNA polymerase* enzyme couples the nucleotides to form a new strand. This process is depicted schematically in Figure 24-23. A similar process transcribes DNA into a complementary molecule of messenger RNA for use by ribosomes as a template for protein synthesis.

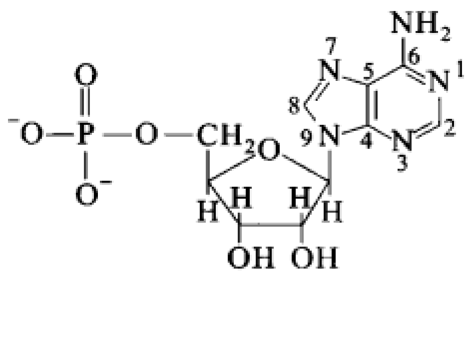
A great deal is known about replication of DNA and translation of the DNA/RNA sequence of bases into proteins. These exciting aspects of nucleic acid chemistry are part of the field of *molecular biology*, and they are covered in detail in biochemistry courses.

24-24 Additional Functions of Nucleotides

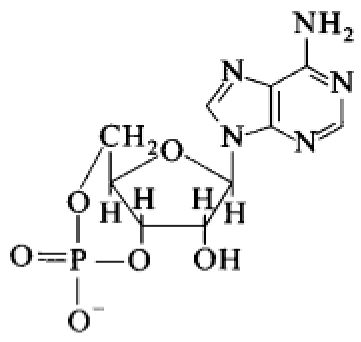
We generally think of nucleotides as the monomers that form DNA and RNA, yet these versatile biomolecules

serve a variety of additional functions. Here we briefly consider a few additional functions.

AMP: A Regulatory Hormone Adenosine monophosphate (AMP) also occurs in a cyclic form, where the 3′- and 5′-hydroxyl groups are both esterified by the same phosphate group. This *cyclic AMP* is involved in transmitting and amplifying the chemical signals of other hormones.

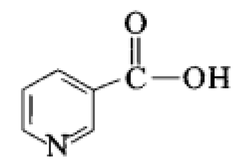


adenosine monophosphate (AMP)
(腺苷酸)

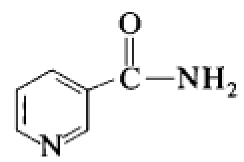


cyclic AMP

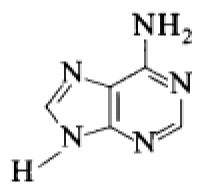
NAD: A Coenzyme Nicotinamide adenine dinucleotide (NAD) is one of the principal oxidation-reduction reagents in biological systems. This nucleotide has the structure of two D-ribose rings (a *di*nucleotide) linked by their 5′ phosphates. The aglycone of one ribose is nicotinamide, and the aglycone of the other is adenine. A dietary deficiency of nicotinic acid (niacin) leads to the disease called *pellagra*, caused by the inability to synthesize enough nicotinamide adenine dinucleotide.



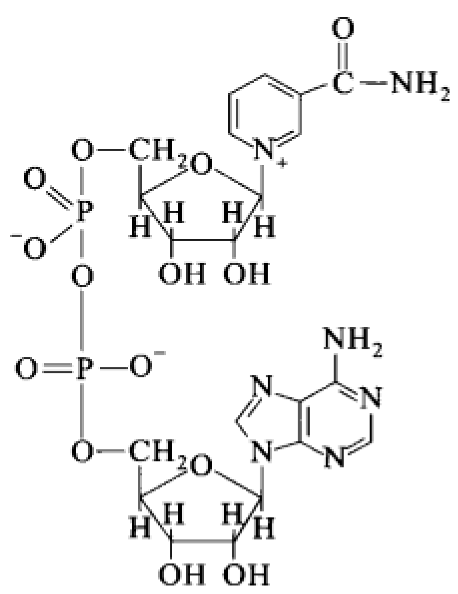
nicotinic acid (烟酸)
(niacin)



nicotinamide
(烟酰胺)



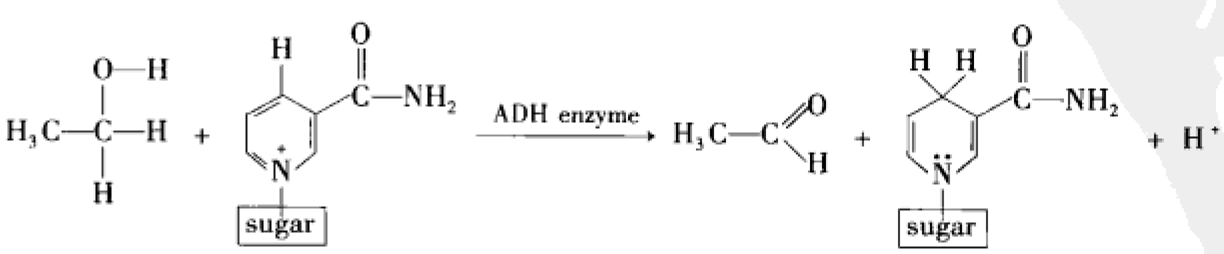
adenine
(腺嘌呤)



NAD^+

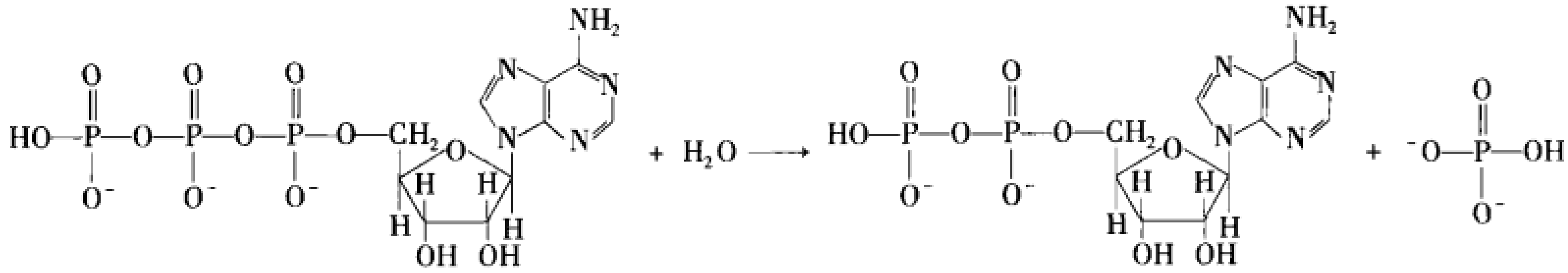
nicotinamide adenine dinucleotide
(烟酰胺腺嘌呤二核苷酸)

The following equation shows how NAD^+ serves as the oxidizing agent in the biological oxidation of an alcohol. Just the nicotinamide portion of NAD shown takes part in the reaction. The enzyme that catalyzes this reaction is called alcohol dehydrogenase (ADH).



ethanol NAD^+ acetaldehyde NADH (reduced)

ATP: An Energy Source When glucose is oxidized in the living cell, the energy released is used to synthesize *adenosine triphosphate* (ATP), an anhydride of phosphoric acid. As with most anhydrides, hydrolysis of ATP is highly exothermic. The hydrolysis products are adenosine diphosphate (ADP) and inorganic phosphate.



adenosine triphosphate (ATP) (腺苷三磷酸)　　adenosine diphosphate (ADP) (腺苷二磷酸)　　phosphate

$\Delta H^{\ominus} = -31$ kJ/mol

Summary in Chinese

本章概要

糖是指脂肪族多羟基醛、多羟基酮或能水解成多羟基醛、酮的化合物，分为单糖、双糖和多糖。

一、单糖的结构与 D、L、α、β 标记

单糖有开链式和氧环式两种结构形式。通常情况下单糖是以氧环式结构存在的半缩醛(酮)结构。

1. 开链结构——Fischer 投影式：在单糖的开链结构中，其 Fischer 投影式，编号最大的手性碳原子上的羟基在右侧为 D 型，反之为 L 型。天然单糖多属 D 系列。

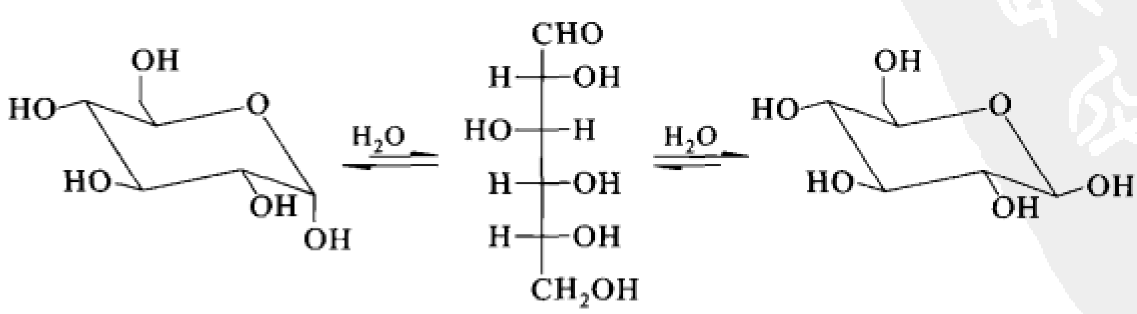
2. 氧环式结构——Haworth 式：戊糖和己糖发生分子内环化形成半缩醛(酮)，使没有手性的羰基碳转变成手性碳原子，产生 α-、β-异构体。新产生的手性碳原子称为苷原子，苷原子上的羟基称为苷羟基。苷羟基与环上编号最大的手性碳原子的羟甲基(如没有羟甲基则看此碳上的氢)处于同侧，则为 β 型；如果处于异侧，则为 α 型。在 Haworth 式中，环上碳原子按命名原则编号(1,2,3,…)，碳原子位次由小到大按顺时针排列时，编号最大的手性碳原子的羟甲基(若无羟甲基，则看氢原子)在环平面上方者为 D 型，在环平面下方者为 L 型。如果按逆时针排列则反之。

二、单糖的化学性质

单糖是多羟基酮、醛，其水溶液中存在开链式结构和氧环式结构的动态平衡，因此，糖既有羰基的性质，如氧化、还原、亲核加成等，又有羟基的性质，如亲核取代、与酸酐反应成酯等，还有半缩醛、酮的性质。由于多官能团的相互影响，单糖还表现出一定的特殊性质，如变旋现象、成脎反应等。

1. 变旋现象：

以葡萄糖为例：



α-异构体　　开链式　　β-异构体

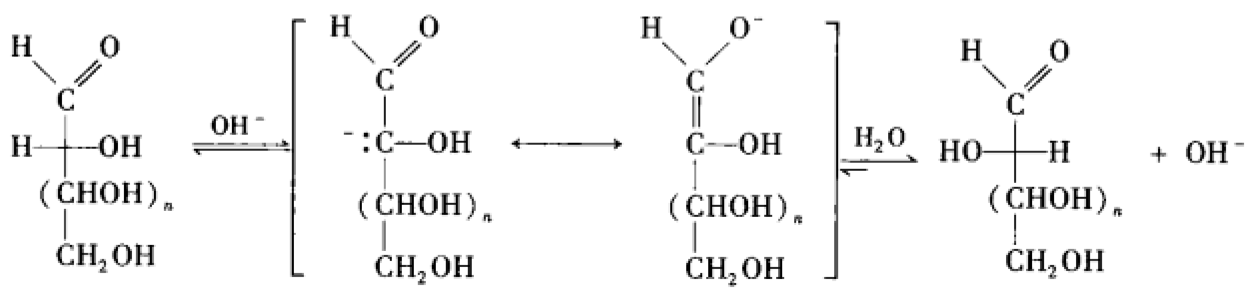
$[\alpha]_D^{25℃} = +112$　　$[\alpha]_D^{25℃} = +18.7$

平衡时　$[\alpha]_D^{25℃} = +52.7$

☆ 在溶液中，α、β 异构体之间的平衡造成测定的旋光值的改变，称为变旋现象。

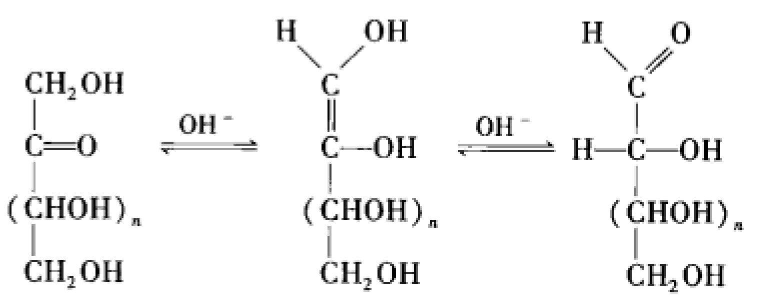
2. 差向异构化和烯二醇重排：

(1) α－碳的差向异构体(epimerzation of the alpha carbon)：



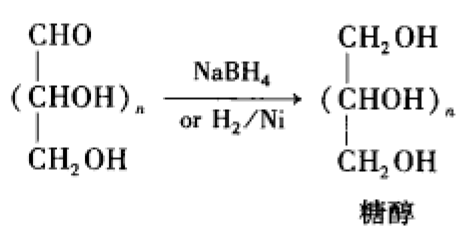
☆ 在多手性中心分子中，由只有一个手性中心的构型不同所产生的异构体叫做差向异构体。在稀碱溶液中，于室温下单糖通过烯醇产生差向异构体的反应称为差向异构化。

(2) 烯二醇重排(enediol rearrangements)：



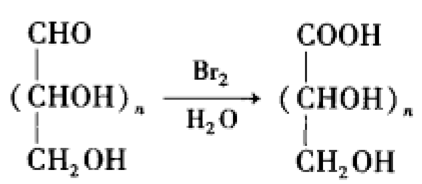
☆ 通过烯二醇中间体，醛糖、酮糖互相转变；不能用 Tollens 试剂(碱性)鉴别醛糖和酮糖。

3. 糖的还原反应：



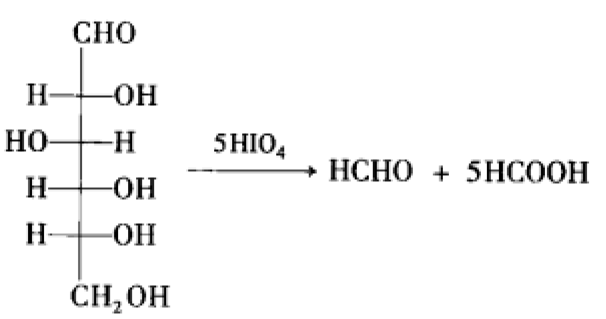
4. 糖的氧化反应：

(1) 被溴水氧化：



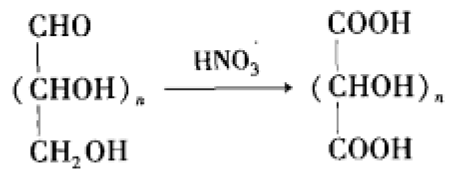
☆ 酮糖不能被溴水氧化，用于鉴别醛糖和酮糖；制备糖酸。

(2) 被 HIO_4 氧化：



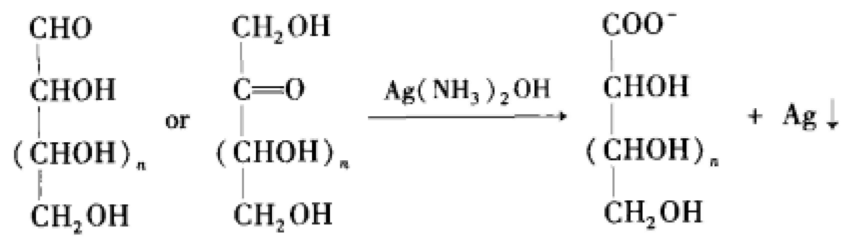
☆ 邻位多元醇的性质；用于推测糖的结构。

(3) 被稀 HNO_3 氧化：



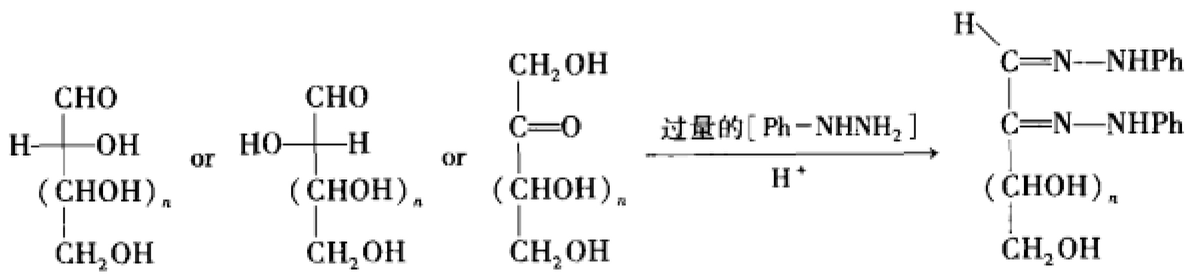
☆ 用于制备糖二酸。

（4）还原糖的 Tollens 试验（Tollens test for reducing sugars）：



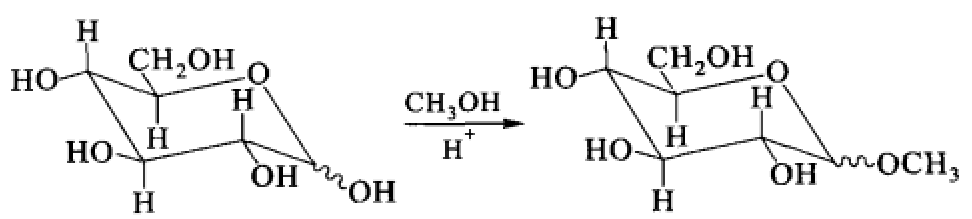
☆ 用于区别还原糖和非还原糖，能被弱氧化剂如 Tollens 试剂氧化的糖称为还原糖，否则称为非还原糖。

（5）与苯肼（phenylhydrazine）反应——生成脎（osazone）：



☆ 用于糖的鉴别、分离；推测糖的结构，C1、C2 构型不同，其他碳的构型相同的糖可生成相同的脎。

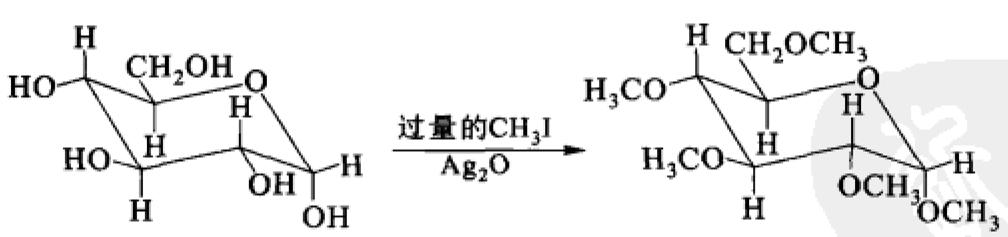
5. 形成糖苷（glycoside）的反应：



α 或 β　　　　α 和 β

☆ 半缩醛的性质；产物糖苷具有缩醛的性质，在碱性介质中稳定，在酸性介质中不稳定，有变旋现象。

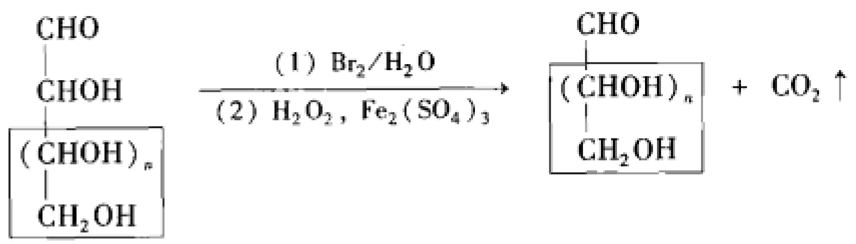
6. 烷基化成醚（alkylation to give ethers）：



☆ 在 $(CH_3)_2SO_4$、NaOH 作用下，也可以成醚。

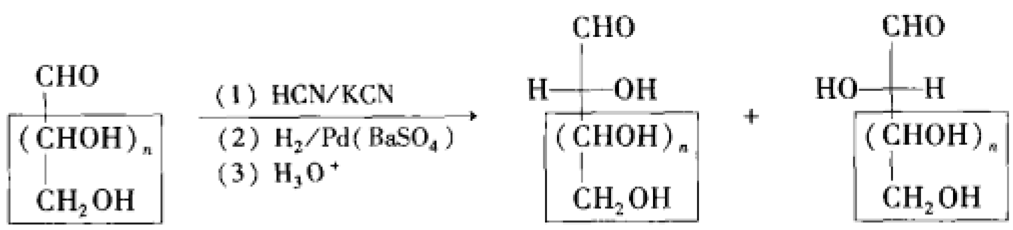
7. 酰基化成酯（acylation to give ethers）：

8. Ruff 降解反应（Ruff degradation）：



☆ 用于由高碳数的糖合成低碳数的糖，即使碳链缩短。

9. Kiliani－Fischer 合成：



☆ 用于合成碳链延伸的糖，即由低碳数的糖合成高碳数的糖。

三、二糖的结构与性质

二糖是两个单糖通过糖苷键连接的，糖苷键可以是由单糖各自的苷羟基之间脱水形成，也可以是一方提供苷羟基而另一方提供羟基脱水而形成的。酶对不同的糖苷键的水解有选择性。如麦芽糖酶只水解 α－葡萄糖苷，苦杏仁酶只水解 β－葡萄糖苷。这种选择性水解的特性可用来判断糖苷键的类型（α 型或 β 型）。蔗糖、麦芽糖、乳糖、纤维二糖是重要的二糖。蔗糖是由 α－D－吡喃葡萄糖与 β－D－呋喃果糖通过两个苷羟基之间脱水而形成的，具有 α－葡萄糖苷－β－果糖苷型糖苷键；麦芽糖是葡萄糖二聚体，是 α－葡萄糖苷羟基与另一分子葡萄糖的 C4 上的羟基脱水而形成的，具有 α－1，4 糖苷键；纤维二糖与麦芽糖几乎相同，只是含 β－1，4 糖苷键；乳糖是由 β－半乳糖与葡萄糖缩合而成，含 β－1，4 糖苷键。麦芽糖、纤维二糖、乳糖分子中均含有苷羟基，是还原糖，能形成脎，有变旋现象。蔗糖分子中不含苷羟基，是非还原性糖，不能成脎，无变旋现象。在蔗糖的水溶液中观察到的旋光变化称为蔗糖的转化。糖水解前后比旋光度发生转变的反应称为糖的转化反应，生成的产物称为转化糖。

四、多糖

多糖是许多个单糖（主要是葡萄糖）通过糖苷键相连构成的。例如，纤维素是 D－葡萄糖通过 β－1，4－糖苷键连接的，而淀粉是 D－葡萄糖通过 α－1，4－糖苷键连接的。淀粉和纤维素是非还原性糖，无变旋现象。

五、核酸

核酸存在于生物细胞中，是酸性物质。核酸分两大类：核糖核酸（RNA）和脱氧核糖核酸（DNA）。核酸是由核苷酸以磷酸二酯键连接起来的生物多聚体。核苷酸由碱基、核糖（脱氧核糖）和磷酸组成。每一种核酸都有四种核苷酸，只在碱基的结构上有变化：对于 RNA 是胞嘧啶（C）、尿嘧啶（U）、腺嘌呤（A）和鸟嘌呤（G）；而对于 DNA，是胞嘧啶（C）、胸腺嘧啶（T）、腺嘌呤（A）和鸟嘌呤（G）。这两种核酸的区别还在于糖单元的种类：对于 RNA 是核糖，而对于 DNA 是脱氧核糖。因为碱基对腺嘌呤－胸腺嘧啶、鸟嘌呤－胞嘧啶和腺嘌呤－尿嘧啶通过特别有利的氢键而配对，核酸能够采取含有互补碱基序列的二聚螺旋结构。在 DNA 复制和 RNA 合成的过程中，DNA 的螺旋结构解旋并发挥模板的功能。

Essential Problem-Solving Skills in Chapter 24

1. Draw the Fischer projection of glucose and the chair conformation of the β anomer of glucose (all substituents equatorial) from memory.
2. Recognize the structures of other anomers and epimers of glucose, drawn as either Fischer projections or chair structures, by noticing the differences from the glucose structure.
3. Correctly name monosaccharides and disaccharides, and draw their structures from their names.

4. Predict which carbohydrates mutarotate, which reduce Tollens reagent, and which undergo epimerization and isomerization under basic conditions. (Those with free hemiacetals will, but glycosides with full acetals will not.)
5. Predict the products of the following reactions of carbohydrates:

bromine in water	NaOH and dimethyl sulfate
nitric acid	acetic anhydride and pyridine
$NaBH_4$ or H_2/Ni	phenylhydrazine
alcohols and H^+	Ruff degradation
CH_3I and Ag_2O	Kiliani-Fischer synthesis

6. Use the information gained from these reactions to determine the structure of an unknown carbohydrate. Use the information gained from methylation and from periodic acid cleavage to determine the ring size.
7. Draw the common types of glycosidic linkages, and recognize these linkages in disaccharides and polysaccharides.
8. Recognize the structures of DNA and RNA, and draw the structures of a ribonucleotide and a deoxyribonucleotide.

Study Problems

24–22 Define each term and give an example.

(**a**) aldose (**b**) ketose (**c**) aldonic acid (**d**) aldaric acid (**e**) glycoside (**f**) aglycone
(**g**) sugar (**h**) anomers (**i**) erythro and threo (**j**) epimers (**k**) furanose (**l**) pyranose
(**m**) Haworth projection (**n**) monosaccharide (**o**) polysaccharide (**p**) disaccharide (**q**) ribonucleoside
(**r**) ribonucleotide (**s**) deoxyribonucleotide (**t**) osazone (**u**) reducing sugar (**v**) amino sugar
(**w**) glycosidic linkage (**x**) an amino sugar (**y**) alditol

24–23 Glucose is the most abundant monosaccharide. From memory, draw glucose in

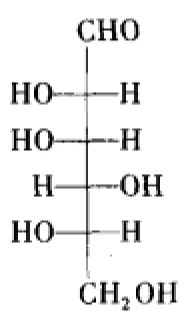
(**a**) the Fischer projection of the open chain
(**b**) the most stable chair conformation of the most stable pyranose anomer
(**c**) the Haworth projection of the most stable pyranose anomer

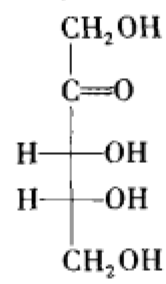
24–24 Without referring to the chapter, draw the chair conformations of

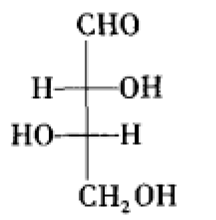
(**a**) β-D-mannopyranose (the C2 epimer of glucose)
(**b**) α-D-allopyranose (the C3 epimer of glucose)
(**c**) β-D-galactopyranose (the C4 epimer of glucose)
(**d**) *N*-acetylglucosamine, glucose with the C2 oxygen atom replaced by an acetylated amino group

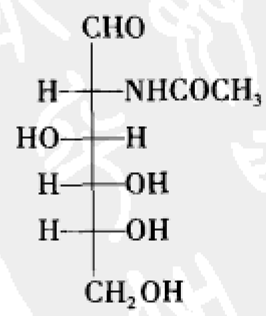
24–25 Classify the following monosaccharides. (*Examples*: D-aldohexose, L-ketotetrose.)

(**a**) (+)-glucose (**b**) (–)-arabinose (**c**) L-fructose

(**d**)

(+)-gulose

(**e**)

(–)-ribulose

(**f**)

(+)-threose

(**g**)

N-acetylglucosamine

24–26 Fructose is the ketose that results from the enediol rearrangement of mannose that shifts the carbonyl group to C2.

(**a**) Propose a mechanism for the enediol rearrangement that converts D-mannose to D-fructose.
(**b**) Draw the α and β anomers of D-fructofuranose. How can you tell which anomer is α and which is β regardless of the

ring size?

24–27 The relative configurations of the stereoisomers of tartaric acid were established by the following syntheses:

1. D-(+)-glyceraldehyde $\xrightarrow{HCN}$ diastereomers A and B (separated).
2. Hydrolysis of A and B using aqueous $Ba(OH)_2$ gave C and D, respectively.
3. HNO_3 oxidation of C and D gave (–)-tartaric acid and *meso*-tartaric acid, respectively.

(a) You know the absolute configuration of D-(+)-glyceraldehyde. Use Fischer projections to show the absolute configurations of products A, B, C, and D.

(b) Show the absolute configurations of the three stereoisomers of tartaric acid: (+)-tartaric acid, (–)-tartaric acid, and *meso*-tartaric acid.

24–28 Use Figure 24–3 (the D family of aldoses) to name the following aldoses.

(a) the C2 epimer of D-arabinose **(b)** the C3 epimer of D-mannose **(c)** the C3 epimer of D-threose
(d) the enantiomer of D-galactose **(e)** the C5 epimer of D-glucose

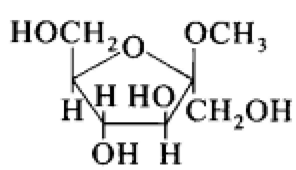
24–29 Draw the following sugar derivatives.

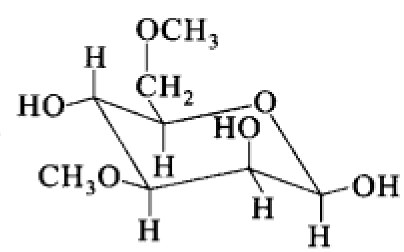
(a) methyl β-D-glucopyranoside **(b)** 2,3,4,6-tetra-*O*-methyl-D-mannopyranose
(c) 1,3,6-tri-*O*-methyl-D-fructofuranose **(d)** methyl 2,3,4,6-tetra-*O*-methyl-β-D-galactopyranoside

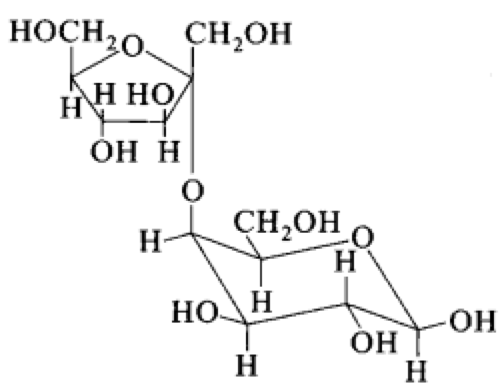
24–30 Draw the structures (using chair conformations of pyranoses) of the following disaccharides.

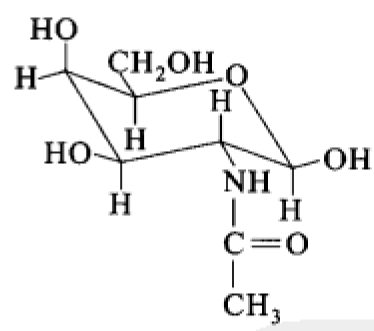
(a) 4-*O*-(α-D-glucopyranosyl)-D-galactopyranose
(b) α-D-fructofuranosyl-β-D-mannopyranoside
(c) 6-*O*-(β-D-galactopyranosyl)-D-glucopyranose

24–31 Give the complete systematic name for each structure.

(a) 

(b) 

(c) 

(d) 

24–32 Which of the sugars mentioned in Problems 24–29, 24–30, and 24–31 are reducing sugars? Which ones would undergo mutarotation?

24–33 Predict the products obtained when D-galactose reacts with each reagent.

(a) Br_2 and H_2O **(b)** NaOH, H_2O **(c)** CH_3OH, H^+ **(d)** $Ag(NH_3)_2^+$ ^-OH
(e) H_2, Ni **(f)** Ac_2O and pyridine **(g)** excess CH_3I, Ag_2O **(h)** $NaBH_4$
(i) Br_2, H_2O, then H_2O_2 and $Fe_2(SO_4)_3$ **(j)** HCN, then H_3O^+, then Na(Hg) **(k)** excess HIO_4

24–34 Draw the structures of the products expected when the following carbohydrates are subjected to methylation followed by acidic hydrolysis. In each case, suggest what reagent would be most appropriate for the methylation step.

(a) D-fructose **(b)** ethyl α-D-glucopyranoside **(c)** sucrose
(d) lactose **(e)** gentiobiose **(f)** chitin

24–35 **(a)** Which of the D-aldopentoses will give optically active aldaric acids on oxidation with HNO_3?

(b) Which of the D-aldotetroses will give optically active aldaric acids on oxidation with HNO_3?

(c) Sugar X is known to be a D-aldohexose. On oxidation with HNO_3, X gives an optically inactive aldaric acid. When X is degraded to an aldopentose, oxidation of the aldopentose gives an optically active aldaric acid. Determine the struc-

ture of X.

(d) Even though sugar X gives an optically inactive aldaric acid, the pentose formed by degradation gives an optically active aldaric acid. Does this finding contradict the principle that optically inactive reagents cannot form optically active products?

(e) Show what product results if the aldopentose formed from degradation of X is further degraded to an aldotetrose. Does HNO_3 oxidize this aldotetrose to an optically active aldaric acid?

24−36 **(a)** Give the products expected when (+)-glyceraldehyde reacts with HCN.

(b) What is the relationship between the products? How might they be separated?

(c) Are the products optically active? Explain.

24−37 When fructose reacts with Tollens reagent, the major products are the carboxylate ions of mannonic acid and gluconic acid.

(a) Propose a mechanism to show how fructose isomerizes to a mixture of glucose and mannose in the presence of Tollens reagent.

(b) Explain why bromine water is a better reagent than Tollens reagent for the oxidation of aldoses to aldonic acids.

24−38 When the gum of the shrub *Sterculia setigera* is subjected to acidic hydrolysis, one of the water-soluble components of the hydrolysate is found to be tagatose. The following information is known about tagatose:

1. Molecular formula $C_6H_{12}O_6$.
2. Undergoes mutarotation.
3. Does not react with bromine water.
4. Reduces Tollens reagent to give D-galactonic acid and D-talonic acid.
5. Methylation of tagatose (using CH_3I and Ag_2O) followed by acidic hydrolysis gives 1,3,4,5-tetra-*O*-methyltagatose.

(a) Draw a Fischer projection structure for the open-chain form of tagatose.

(b) Draw the most stable conformation of the most stable cyclic hemiacetal form of tagatose.

24−39 After a series of Kiliani-Fischer syntheses on (+)-glyceraldehyde, an unknown sugar is isolated from the reaction mixture. The following experimental information is obtained:

1. Molecular formula $C_6H_{12}O_6$.
2. Undergoes mutarotation.
3. Reacts with bromine water to give an aldonic acid.
4. Reacts with phenylhydrazine to give an osazone, mp 178 ℃.
5. Reacts with HNO_3 to give an optically active aldaric acid.
6. Ruff degradation followed by HNO_3 oxidation gives an optically inactive aldaric acid.
7. Two Ruff degradations followed by HNO_3 oxidation give *meso*-tartaric acid.
8. Formation of the methyl glycoside (using CH_3OH and HCl), followed by periodic acid oxidation, gives a mixture of products that includes (+)-glyceraldehyde.

(a) Draw a Fischer projection for the open-chain form of this unknown sugar. Use Figure 24−3 to name the sugar.

(b) Draw the most stable conformation of the most stable cyclic hemiacetal form of this sugar, and give the structure a complete systematic name.

24−40 An unknown reducing disaccharide is found to be unaffected by invertase enzymes. Treatment with an α-galactosidase cleaves the disaccharide to give one molecule of D-fructose and one molecule of D-galactose. When the disaccharide is treated with iodomethane and silver oxide and then hydrolyzed in dilute acid, the products are 2,3,4,6-tetra-*O*-methylgalactose and 1,3,4-tri-*O*-methylfructose. Propose a structure for this disaccharide, and give its complete systematic name.

24−41 Draw the structures of the following nucleotides.

(a) guanosine triphosphate (GTP)

(b) deoxycytidine monophosphate (dCMP)

(c) cyclic guanosine monophosphate (cGMP)

24−42 Draw the structure of a four-residue segment of DNA with the following sequence.

(3′ end) G−T−A−C (5′ end)

24−43 Erwin Chargaff's discovery that DNA contains equimolar amounts of guanine and cytosine and also equimolar amounts of

adenine and thymine has come to be known as *Chargaff's rule*:

$$G = C \text{ and } A = T$$

(a) Does Chargaff's rule imply that equal amounts of guanine and adenine are present in DNA? That is, does $G = A$?

(b) Does Chargaff's rule imply that the sum of the purine residues equals the sum of the pyrimidine residues? That is, does $A + G = C + T$?

(c) Does Chargaff's rule apply only to double-stranded DNA, or would it also apply to each individual strand if the double helical strand were separated into its two complementary strands?

Chapter 25

Amino Acids, Peptides, and Proteins

25－1 Introduction

Proteins are the most abundant organic molecules in animals, playing important roles in all aspects of cell structure and function. Proteins are biopolymers of **α-amino acids**, so named because the amino group is bonded to the α carbon atom, next to the carbonyl group. The physical and chemical properties of a protein are determined by its constituent amino acids. The individual amino acid subunits are joined by amide linkages called **peptide bonds**. Figure 25－1 shows the general structure of an α-amino acid and a protein.

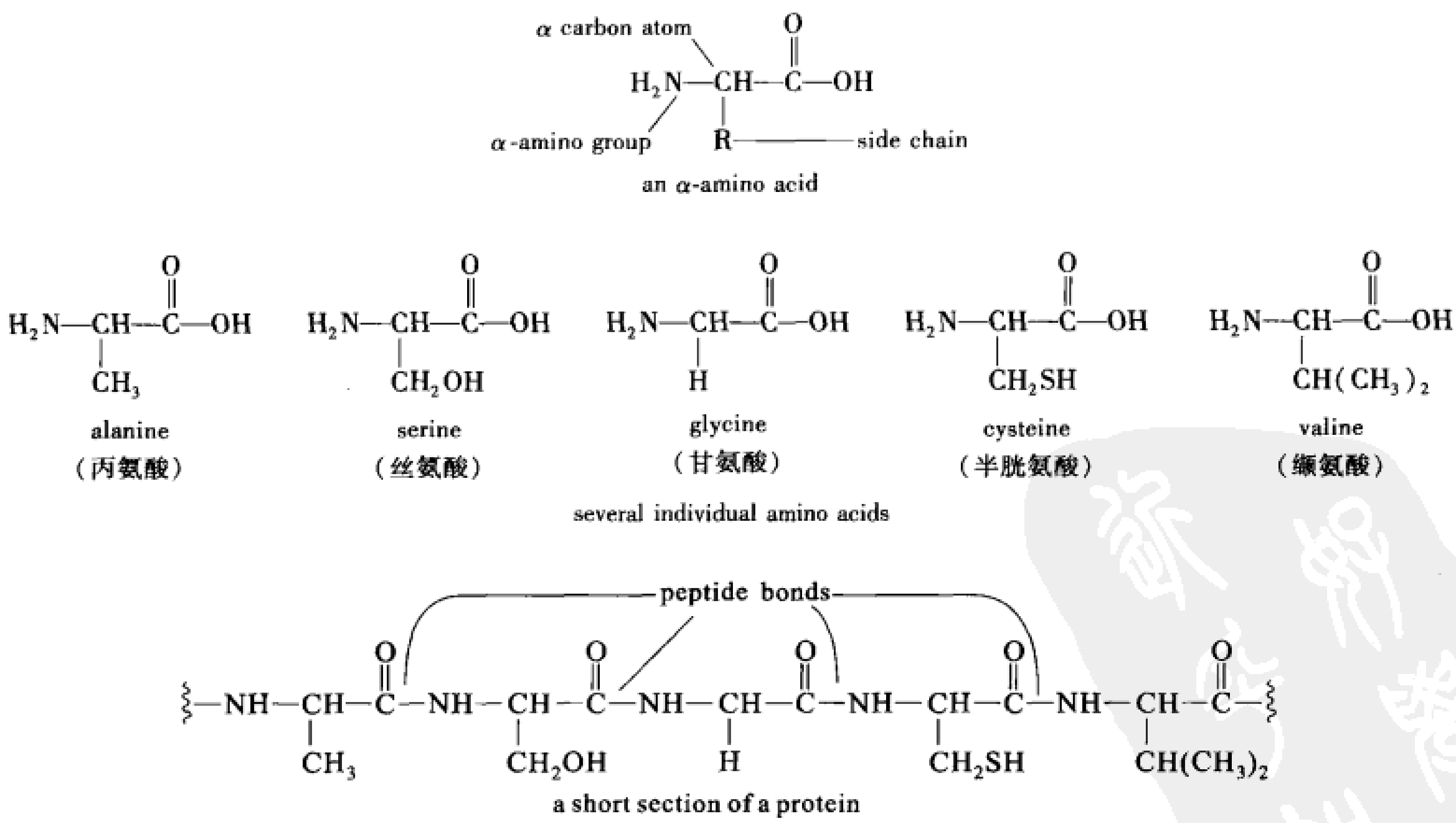


Figure 25－1 Structure of a general protein and its constituent amino acids.

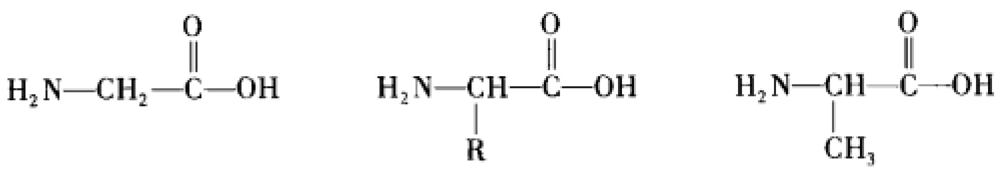
Proteins have an amazing range of structural and catalytic properties as a result of their varying amino acid composition. Because of this versatility, proteins serve an astonishing variety of functions in living organisms. Some of the functions of the major classes of proteins are outlined in Table 25－1.

TABLE 25-1 Examples of Protein Functions		
Class of Protein	**Example**	**Function of Example**
structural proteins	collagen, keratin(胶原蛋白,角蛋白)	Strengthen tendons, skin, hair, nails
enzymes	DNA polymerase(DNA 聚合酶)	Replicates and repairs DNA
transport proteins	Hemoglobin(血红蛋白)	Transports O_2 to the cells
contractile proteins	actin, myosin(肌动蛋白,肌球蛋白)	Cause contraction of muscles
protective proteins	Antibodies(抗体)	Complex with foreign proteins
hormones	Insulin(胰岛素)	Regulates glucose metabolism
toxins(毒素)	snake venoms	Incapacitate prey

The study of proteins is one of the major branches of biochemistry, and there is no clear division between the organic chemistry of proteins and their biochemistry. In this chapter, we begin the study of proteins by learning about their constituents, the amino acids. We also discuss how amino acid monomers are linked into the protein polymer, and how the properties of a protein depend on those of its constituent amino acids. These concepts are needed for the further study of protein structure and function in a biochemistry course.

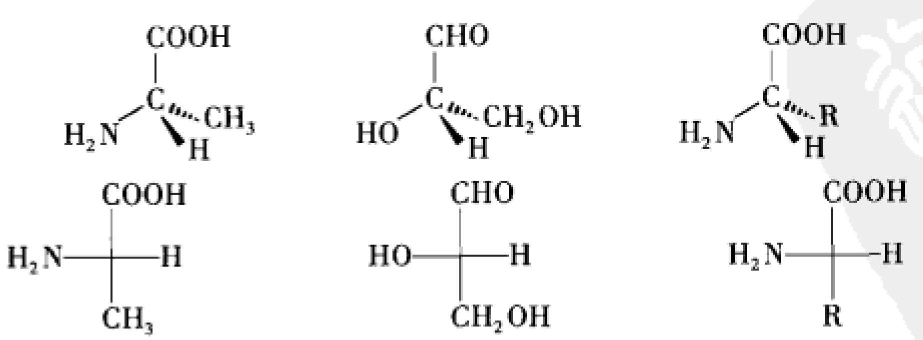
25-2 Structure and Stereochemistry of the α-Amino Acids

The term **amino acid** might mean any molecule containing both an amino group and any type of acid group; however, the term is almost always used to refer to an α-amino carboxylic acid. The simplest α-amino acid is aminoacetic acid, called *glycine*. Other common amino acids have side chains (symbolized by R) substituted on the α carbon atom. For example, alanine is the amino acid with a methyl side chain.



glycine (甘氨酸) a substituted amino acid alanine ($R = CH_3$) (丙氨酸)

Except for glycine, the α-amino acids are all chiral. In every case (except glycine), the chirality center is the asymmetric α carbon atom. Nearly all the naturally occurring amino acids are found to have the (S) configuration at the α carbon atom. Figure 25-2 shows a Fischer projection of the (S) enantiomer of alanine, with the carbon chain along the vertical and the carbonyl carbon at the top. Notice that the configuration of (S)-alanine is similar to that of L-(−)-glyceraldehyde, with the amino group on the left in the Fischer projection. Because their stereochemistry is similar to that of L-(−)-glyceraldehyde, the naturally occurring (S)-amino acids are classified as **L-amino acids**.



L-alanine(丙氨酸) (S)-alanine L-(−)-glyceraldehyde(甘油醛) (S)-glyceraldehyde an L-amino acid (S) configuration

Figure 25-2 Almost all the naturally occurring amino acids have the (S) configuration, with stereochemistry resembling that of L-(−)-glyceraldehyde. They are therefore called L-amino acids.

Although D-amino acids are occasionally found in nature, we usually assume the amino acids under discussion are the common L-amino acids. Remember once again that the D and L nomenclature, like the *R* and *S* designation, gives the configuration of the asymmetric carbon atom. It does not imply the sign of the optical rotation, (+) or (−), which must be determined experimentally.

Amino acids combine many of the properties and reactions of both amines and carboxylic acids. The combination of a basic amino group and an acidic carboxyl group in the same molecule also results in some unique properties and reactions. The side chains of some amino acids also have functional groups that lend interesting properties and undergo reactions of their own.

25−2A The Standard Amino Acids of Proteins

There are 20 α-amino acids, called the **standard amino acids**, that are found in nearly all proteins. The standard amino acids differ from each other in the structure of the side chains bonded to their α carbon atoms. All the standard amino acids are L-amino acids. Table 25−2 shows the 20 standard amino acids, grouped according to the chemical properties of their side chains. Each amino acid is given a three-letter abbreviation and a one-letter symbol for use in writing protein structures.

Notice in Table 25−2 how proline is different from the other standard amino acids. Its amino group is fixed in a ring with its α carbon atom. This cyclic structure lends additional strength and rigidity to proline-containing peptides.

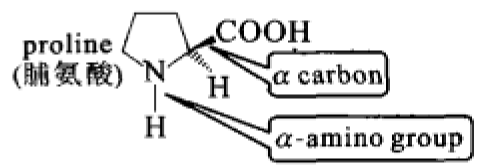
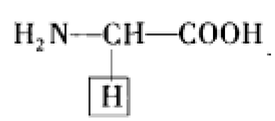
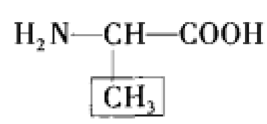
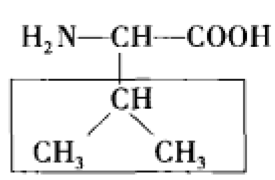
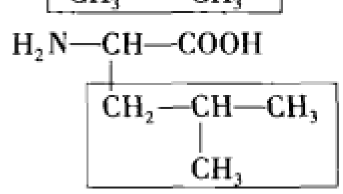
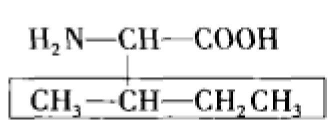
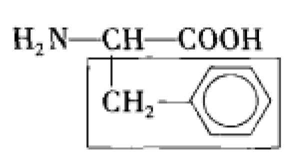
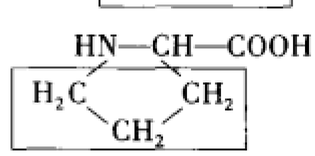
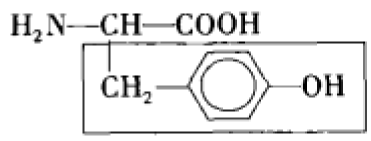
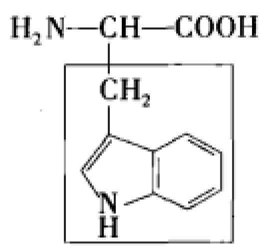
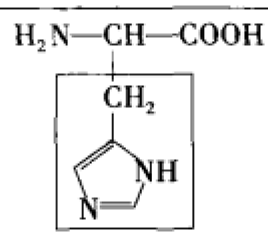


TABLE 25−2 The Standard Amino Acids

Name	Symbol	Abbreviation	Structure	Functional Group in Side Chain	Isoelectric Point (等电点)
side chain is H or alkyl (nonpolar)					
glycine (甘氨酸)	G	Gly		none	6.0
alanine (丙氨酸)	A	Ala		alkyl group	6.0
*valine (缬氨酸)	V	Val		alkyl group	6.0
*leucine (亮氨酸)	L	Leu		alkyl group	6.0
*isoleucine (异亮氨酸)	I	Ile		alkyl group	6.0
*phenylalanine (苯丙氨酸)	F	Phe		aromatic group	5.5
proline (脯氨酸)	P	Pro		rigid cyclic structure	6.3

Continue

Name	Symbol	Abbreviation	Structure	Functional Group in Side Chain	Isoelectric Point（等电点）
side chain contains an —OH					
serine（丝氨酸）	S	Ser	$H_2N—CH—COOH$, side chain $CH_2—OH$	hydroxyl group	5.7
*threonine（苏氨酸）	T	Thr	$H_2N—CH—COOH$, side chain $HO—CH—CH_3$	hydroxyl group	5.6
tyrosine（酪氨酸）	Y	Tyr		phenolic —OH group	5.7
side chain contains sulfur					
cysteine（半胱氨酸）	C	Cys	$H_2N—CH—COOH$, side chain $CH_2—SH$	thiol	5.0
*methionine（蛋氨酸）	M	Met	$H_2N—CH—COOH$, side chain $CH_2—CH_2—S—CH_3$	sulfide	5.7
side chain contains nonbasic nitrogen					
asparagine（天冬酰胺）	N	Asn	$H_2N—CH—COOH$, side chain $CH_2—C(=O)—NH_2$	amide	5.4
glutamine（谷氨酰胺）	Q	Gln	$H_2N—CH—COOH$, side chain $CH_2—CH_2—C(=O)—NH_2$	amide	5.7
*tryptophan（色氨酸）	W	Trp		indole(吲哚)	5.9
side chain is acidic					
aspartic acid（天冬氨酸）	D	Asp	$H_2N—CH—COOH$, side chain $CH_2—COOH$	carboxylic acid	2.8
glutamic acid（谷氨酸）	E	Glu	$H_2N—CH—COOH$, side chain $CH_2—CH_2—COOH$	carboxylic acid	3.2
side chain is basic					
*lysine（赖氨酸）	K	Lys	$H_2N—CH—COOH$, side chain $CH_2—CH_2—CH_2—CH_2—NH_2$	amino group	9.7
*arginine（精氨酸）	R	Arg	$H_2N—CH—COOH$, side chain $CH_2—CH_2—CH_2—NH—C(=NH)—NH_2$	guanidino group（胍基）	10.8
*histidine（组氨酸）	H	His		imidazole ring（咪唑环）	7.6

*essential amino acid

PROBLEM 25-1

Draw three-dimensional representations of the following amino acids.

(a) L-phenylalanine **(b)** L-arginine **(c)** D-serine **(d)** L-tryptophan

PROBLEM 25-2

Most naturally occurring amino acids have chirality centers (the asymmetric α carbon atoms) that are named (S) by the Cahn-Ingold-Prelog convention. The common naturally occurring form of cysteine has a chirality center that is named (R), however.

(a) What is the relationship between (R)-cysteine and (S)-alanine? Do they have the opposite three-dimensional configuration (as the names might suggest) or the same configuration?

(b) (S)-alanine is an L-amino acid (Figure 25-2). Is (R)-cysteine a D-amino acid or an L-amino acid?

25-2B Essential Amino Acids

Human beings can synthesize about half of the amino acids needed to make proteins. Other amino acids, called the **essential amino acids**, must be provided in the diet. The ten essential amino acids, starred(*) in Table 25-2, are the following:

arginine (Arg)	valine (Val)	methionine (Met)	leucine (Leu)
threonine (Thr)	phenylalanine (Phe)	histidine (His)	isoleucine (Ile)
lysine (Lys)	tryptophan (Trp)		

Proteins that provide all the essential amino acids in about the right proportions for human nutrition are called **complete proteins**. Examples of complete proteins are those in meat, fish, milk, and eggs. About 50 g of complete protein per day is adequate for adult humans.

Proteins that are severely deficient in one or more of the essential amino acids are called **incomplete proteins**. If the protein in a person's diet comes mostly from one incomplete source, the amount of human protein that can be synthesized is limited by the amounts of the deficient amino acids. Plant proteins are generally incomplete. Rice, corn, and wheat are all deficient in lysine. Rice also lacks threonine, and corn also lacks tryptophan. Beans, peas, and other legumes have the most complete proteins among the common plants, but they are deficient in methionine.

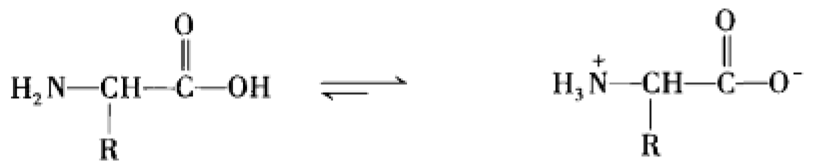
Vegetarians can achieve an adequate intake of the essential amino acids if they eat many different plant foods. Plant proteins can be chosen to be complementary, with some foods supplying amino acids that others lack. An alternative is to supplement the vegetarian diet with a rich source of complete protein such as milk or eggs.

PROBLEM 25-3

The herbicide *glyphosate* (Roundup®) kills plants by inhibiting an enzyme needed for synthesis of phenylalanine. Deprived of phenylalanine, the plant cannot make the proteins it needs, and it gradually weakens and dies. Although a small amount of glyphosate is deadly to a plant, its human toxicity is quite low. Suggest why this powerful herbicide has little effect on humans.

25−3 Acid-Base Properties of Amino Acids

Although we commonly write amino acids with an intact carboxyl (—COOH) group and amino (—NH_2) group, their actual structure is ionic and depends on the pH. The carboxyl group loses a proton, giving a carboxylate ion, and the amino group is protonated to an ammonium ion. This structure is called a **dipolar ion** or a **zwitterion** (German for "dipolar ion").



uncharged structure (minor component) — dipolar ion, or zwitterion(两性离子) (major component)

The dipolar nature of amino acids gives them some unusual properties:

1. Amino acids have **high melting points**, generally over 200 ℃.

$$H_3\overset{+}{N}—CH_2—COO^-$$

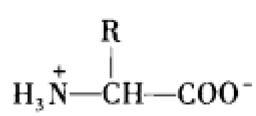
glycine, mp 262 ℃
(甘氨酸)

2. Amino acids are more **soluble in water** than they are in ether, dichloromethane, and other common organic solvents.

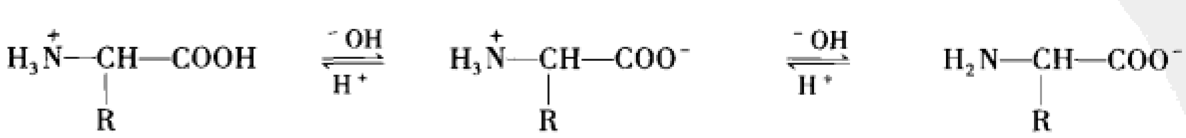
3. Amino acids have much **larger dipole moments** (μ) than simple amines or simple acids.

$H_3\overset{+}{N}—CH_2—COO^-$	$CH_3—CH_2—CH_2—NH_2$	$CH_3—CH_2—COOH$
glycine, $\mu = 14D$	propylamine, $\mu = 1.4D$	propionic acid, $\mu = 1.7D$

4. Amino acids are **less acidic than most carboxylic acids** and **less basic than most amines**. In fact, the acidic part of the amino acid molecule is the —NH_3^+ group, not a —COOH group. The basic part is the —COO^- group, and not a free —NH_2 group.

R—COOH	R—NH_2	
$pK_a = 5$	$pK_b = 4$	$pK_a = 10$ $pK_b = 12$

Because amino acids contain both acidic (—NH_3^+) and basic (—COO^-) groups, they are *amphoteric* (having both acidic and basic properties). The predominant form of the amino acid depends on the pH of the solution. In an acidic solution, the —COO^- group is protonated to a free —COOH group, and the molecule has an overall positive charge. As the pH is raised, the —COOH loses its proton at about pH 2. This point is called pK_{a1}, the first acid-dissociation constant. As the pH is raised further, the —NH_3^+ group loses its proton at about pH 9 or 10. This point is called pK_{a2}, the second acid-dissociation constant. Above this pH, the molecule has an overall negative charge.



cationic in acid — $pK_{a1} \approx 2$ — neutral — $pK_{a2} \approx 9-10$ — anionic in base

Figure 25−3 shows a titration curve for glycine. The curve starts at the bottom left, where glycine is entirely in its cationic form. Base is slowly added, and the pH is recorded. At pH 2.3, half of the cationic form has been converted to the zwitterionic form. At pH 6.0, essentially all the glycine is in the zwitterionic form. At pH 9.6, half of the zwitterionic form has been converted to the basic form. From this graph, we can see that glycine is mostly in the cationic form at pH values below 2.3, mostly in the anionic form at pH values above 9.6, and mostly in the zwitterionic form at pH values between 2.3 and 9.6. By varying the pH of the solution, we can control the charge on the molecule. This ability to control the charge of an amino acid is useful for separating and identifying amino acids by electrophoresis, as described in Section 25−4.

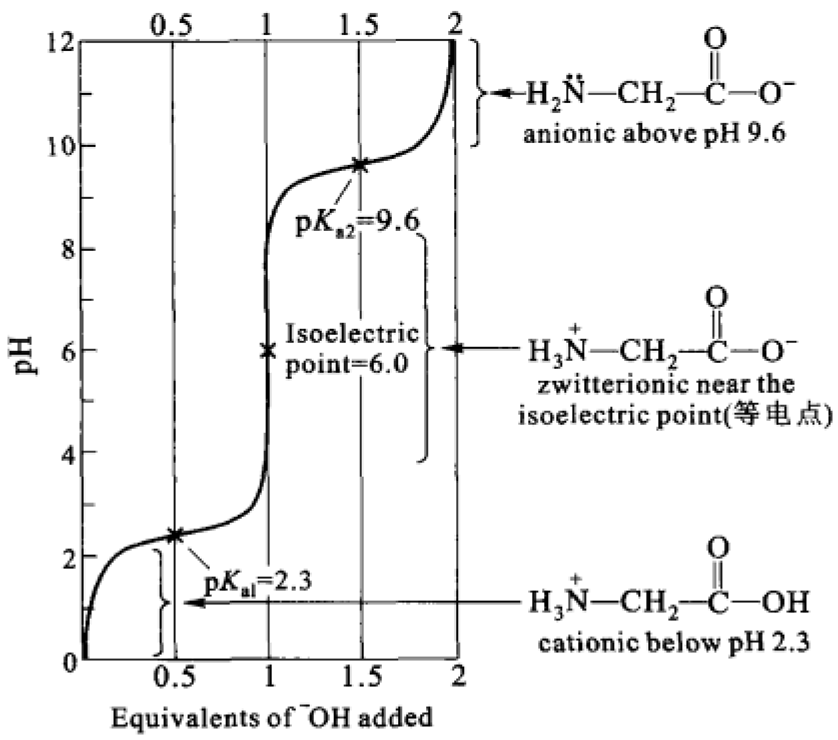


Figure 25−3 A titration curve for glycine.

25−4 Isoelectric Points

An amino acid bears a positive charge in acidic solution (low pH) and a negative charge in basic solution (high pH). There must be an intermediate pH where the amino acid is evenly balanced between the two forms, as the dipolar zwitterion with a net charge of zero. This pH is called the **isoelectric pH** or the **isoelectric point**.

The isoelectric points of the standard amino acids are given in Table 25−2. Notice that the isoelectric pH depends on the amino acid structure in a predictable way.

acidic amino acids:	aspartic acid (2.8), glutamic acid (3.2)
neutral amino acids:	(5.0 to 6.3)
basic amino acids:	lysine (9.7), arginine (10.8), histidine (7.6)

The side chains of aspartic acid and glutamic acid contain acidic carboxyl groups. These amino acids have acidic isoelectric points around pH 3. An acidic solution is needed to prevent deprotonation of the second carboxylic acid group and to keep the amino acid in its neutral isoelectric state.

Basic amino acids (histidine, lysine, and arginine) have isoelectric points at pH values of 7.6, 9.7, and 10.8, respectively. These values reflect the weak basicity of the imidazole ring, the intermediate basicity of an amino group, and the strong basicity of the guanidino group. A basic solution is needed in each case to prevent

protonation of the basic side chain to keep the amino acid electrically neutral.

The other amino acids are considered neutral, with no strongly acidic or basic side chains. Their isoelectric points are slightly acidic (from about 5 to 6) because the $—NH_3^+$ group is slightly more acidic than the $—COO^-$ group is basic.

PROBLEM 25−4

Draw the structure of the predominant form of

(**a**) valine at pH 11 (**b**) proline at pH 2

(**c**) arginine at pH 7 (**d**) glutamic acid at pH 7

(**e**) a mixture of alanine, lysine, and aspartic acid at (i) pH 6; (ii) pH 11; (iii) pH 2

PROBLEM 25−5

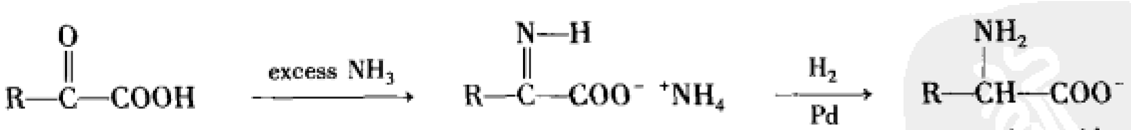
Draw the resonance forms of a protonated guanidino group, and explain why arginine has such a strongly basic isoelectric point.

25−5 Synthesis of Amino Acids

Naturally occurring amino acids can be obtained by hydrolyzing proteins and separating the amino acid mixture. Even so, it is often less expensive to synthesize the pure amino acid. In some cases, an unusual amino acid or an unnatural enantiomer is needed, and it must be synthesized. In this chapter, we consider four methods for making amino acids. All these methods are extensions of reactions we have already studied.

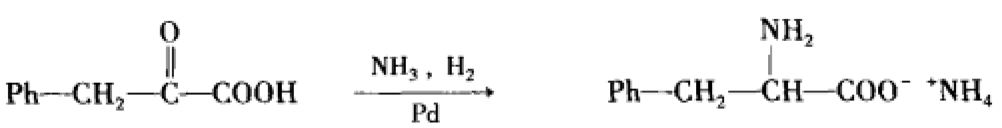
25−5A Reductive Amination

Reductive amination of ketones and aldehydes is one of the best methods for synthesizing amines. It also forms amino acids. When an α-ketoacid is treated with ammonia, the ketone reacts to form an imine. The imine is reduced to an amine by hydrogen and a palladium catalyst. Under these conditions, the carboxylic acid is not reduced.



α-ketoacid(α-酮酸) imine(亚胺) α-amino acid

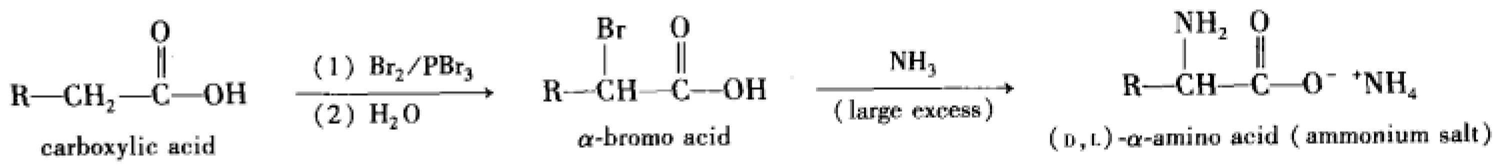
This entire synthesis is accomplished in one step by treating the α-ketoacid with ammonia and hydrogen in the presence of a palladium catalyst. The product is a racemic α-amino acid. The following reaction shows the synthesis of racemic phenylalanine from 3-phenyl-2-oxopropanoic acid.



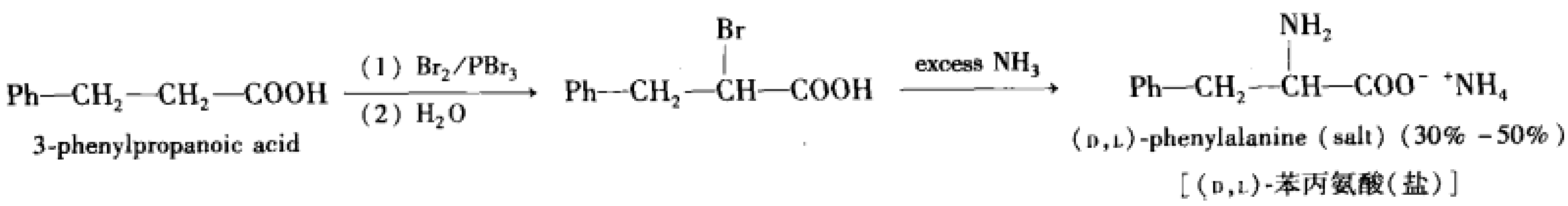
3-phenyl-2-oxopropanoic acid (D,L)-phenylalanine (ammonium salt) (30%)
[苯丙氨酸(铵盐)]

25-5B Amination of an α-Halo Acid

The Hell-Volhard-Zelinsky reaction is an effective method for introducing bromine at the α position of a carboxylic acid. The racemic α-bromo acid is converted to a racemic α-amino acid by direct amination, using a large excess of ammonia.

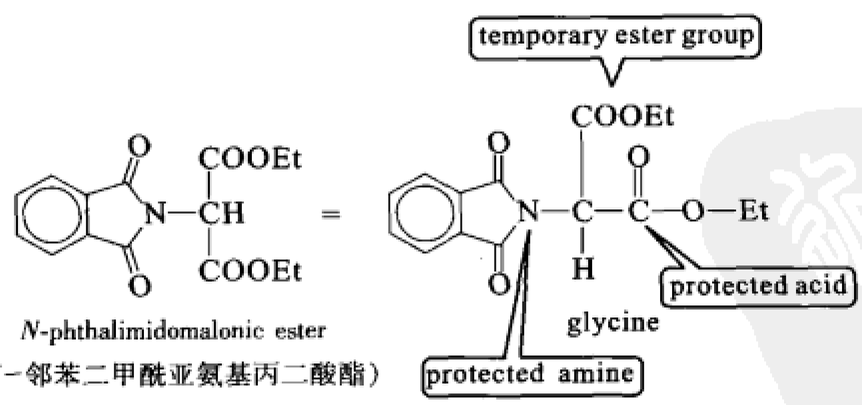


In Section 20-17, we saw that direct alkylation is often a poor synthesis of amines, giving large amounts of overalkylated products. In this case, however, the reaction gives acceptable yields because a large excess of ammonia is used, making ammonia the nucleophile that is most likely to displace bromine. Also, the adjacent carboxylate ion in the product reduces the nucleophilicity of the amino group. The following sequence shows bromination of 3-phenylpropanoic acid, followed by displacement of bromide ion, to form the ammonium salt of racemic phenylalanine.



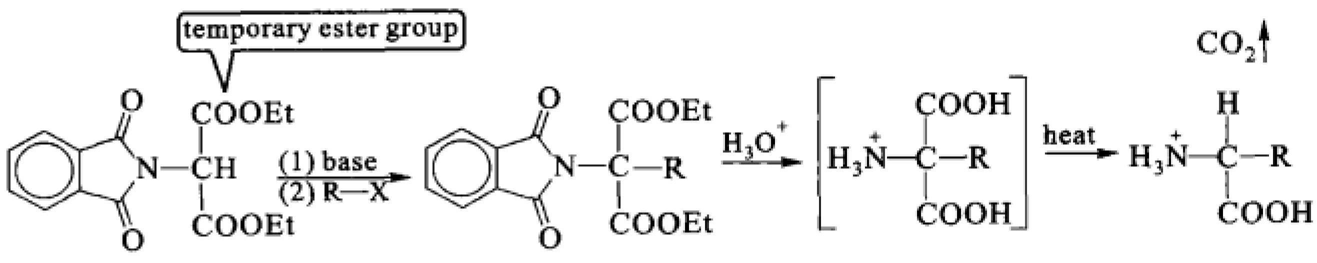
25-5C The Gabriel-Malonic Ester Synthesis

The Gabriel-malonic ester synthesis begins with *N*-phthalimidomalonic ester. Think of *N*-phthalimidomalonic ester as a molecule of glycine (aminoacetic acid) with the amino group protected as an amide (a phthalimide in this case) to keep it from acting as a nucleophile. The acid is protected as an ethyl ester, and the α position is further activated by the additional (temporary) ester group of diethyl malonate.



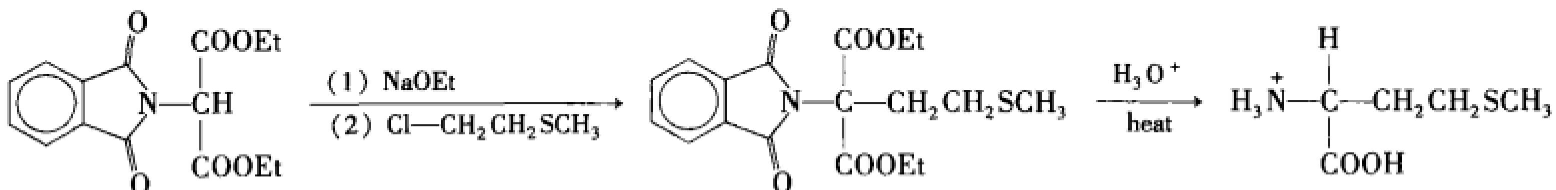
Just as the malonic ester synthesis gives substituted acetic acids, the *N*-phthalimidomalonic ester synthesis gives substituted aminoacetic acids: α-amino acids. *N*-phthalimidomalonic ester is alkylated in the same way as malonic ester. When the alkylated *N*-phthalimidomalonic ester is hydrolyzed, the phthalimido group is hydrolyzed along with the ester groups. The product is an alkylated aminomalonic acid. Decarboxylation gives a racemic α-amino acid.

The Gabriel-malonic ester synthesis



N-phthalimidomalonic ester (N-邻苯二甲酰亚氨基丙二酸酯) alkylated (烷基化) hydrolyzed (水解) α-amino acid

The Gabriel-malonic ester synthesis is used to make many amino acids that cannot be formed by direct amination of haloacids. The following example shows the synthesis of methionine, which is formed in very poor yield by direct amination.

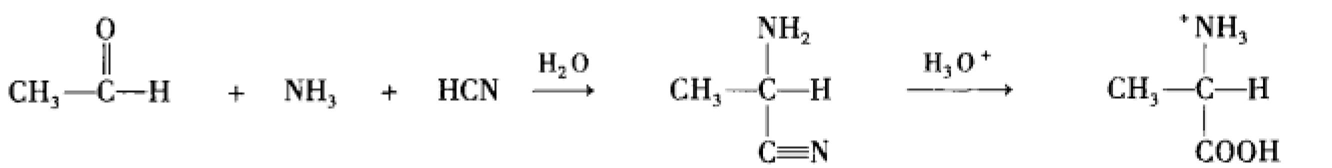


(D,L)-methionine(蛋氨酸)
(50%)

25-5D The Strecker Synthesis

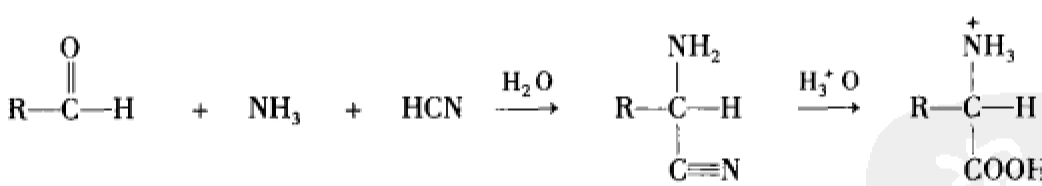
The first known synthesis of an amino acid occurred in 1 850 in the laboratory of Adolph Strecker in Tübingen, Germany. Strecker added acetaldehyde to an aqueous solution of ammonia and HCN. The product was α-amino propionitrile, which Strecker hydrolyzed to racemic alanine.

The Strecker synthesis of alanine



acetaldehyde α-amino propionitrile (α-氨基丙腈) (D,L)-alanine(丙氨酸) (60%)

The **Strecker synthesis** can form a large number of amino acids from appropriate aldehydes.



aldehyde α-amino nitrile α-amino acid

PROBLEM 25-6

Show how the Gabriel-malonic ester synthesis could be used to make

(a) valine (b) phenylalanine (c) glutamic acid (d) leucine

PROBLEM 25-7

Show how you would use a Strecker synthesis to make

(a) leucine (b) glycine (c) valine

25−6 Resolution of Amino Acids

All the laboratory syntheses of amino acids described in Section 25−5 produce racemic products. In most cases, only the L enantiomers are biologically active. The D enantiomers may even be toxic. Pure L enantiomers are needed for peptide synthesis if the product is to have the activity of the natural material. Therefore, we must be able to resolve a racemic amino acid into its enantiomers.

In many cases, amino acids can be resolved by the methods we have already discussed. If a racemic amino acid is converted to a salt with an optically pure chiral acid or base, two diastereomeric salts are formed. These salts can be separated by physical means such as selective crystallization or chromatography. Pure enantiomers are then regenerated from the separated diastereomeric salts. Strychnine and brucine are naturally occurring optically active bases, and tartaric acid is used as an optically active acid for resolving racemic mixtures.

Enzymatic resolution is also used to separate the enantiomers of amino acids. Enzymes are chiral molecules with specific catalytic activities. For example, when an acylated amino acid is treated with an enzyme like hog kidney acylase or carboxypeptidase, the enzyme cleaves the acyl group from just the molecules having the natural (L) configuration. The enzyme does not recognize D-amino acids, so they are unaffected. The resulting mixture of acylated D-amino acid and deacylated L-amino acid is easily separated. Figure 25−4 shows how this selective enzymatic deacylation is accomplished.

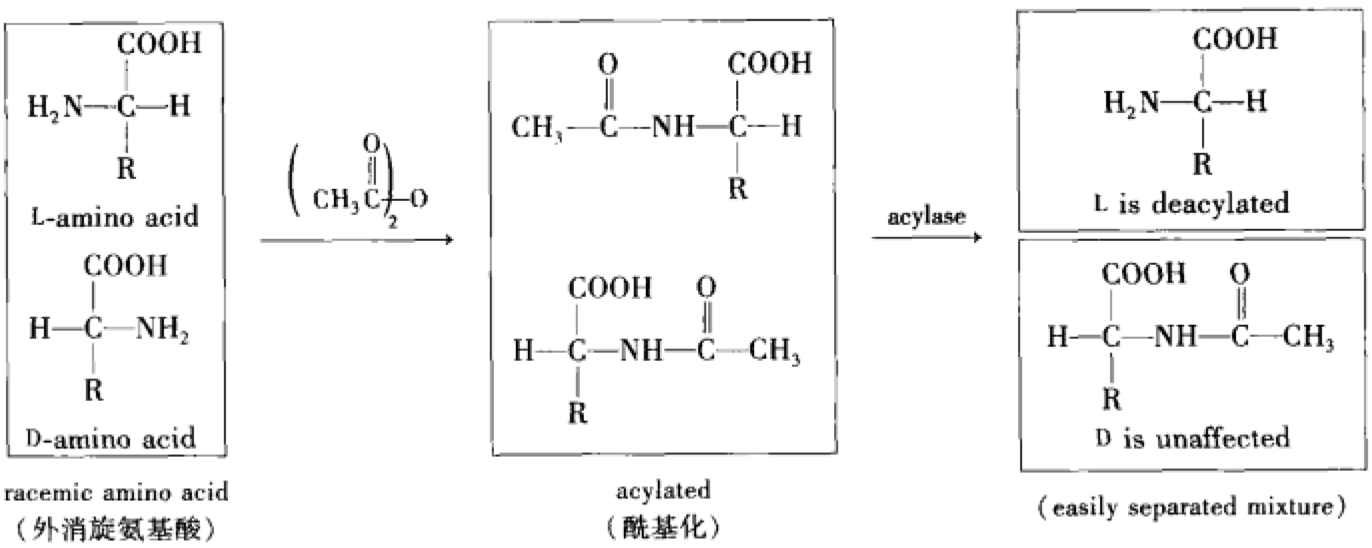


Figure 25−4 Selective enzymatic deacylation.

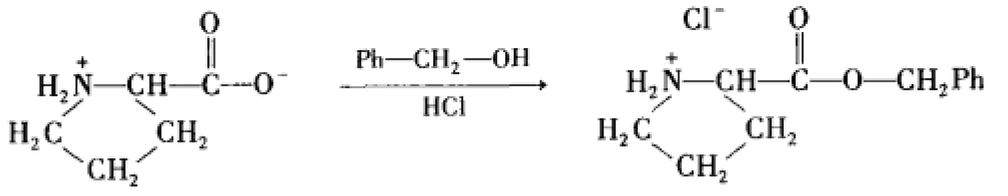
25−7 Reactions of Amino Acids

Amino acids undergo many of the standard reactions of both amines and carboxylic acids. Conditions for some of these reactions must be carefully selected, however, so that the amino group does not interfere with a carboxyl group reaction, and vice versa. We will consider two of the most useful reactions, esterification of the carboxyl group and acylation of the amino group. These reactions are often used to protect either the carboxyl group or the amino group while the other group is being modified or coupled to another amino acid. Amino acids also undergo reactions that are specific to the α-amino acid structure.

25−7A Esterification of the Carboxyl Group

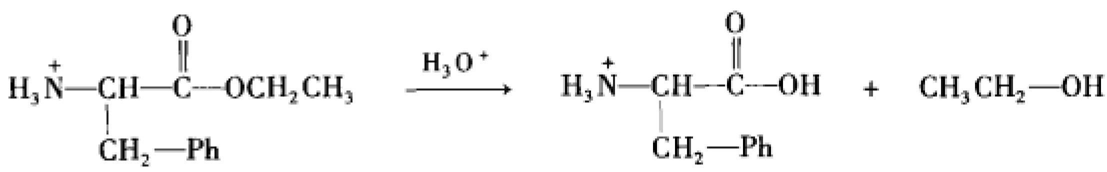
Like monofunctional carboxylic acids, amino acids are esterified by treatment with a large excess of an alcohol

and an acidic catalyst (often gaseous HCl). Under these acidic conditions, the amino group is present in its protonated ($-NH_3^+$) form, so it does not interfere with esterification. The following example illustrates esterification of an amino acid.



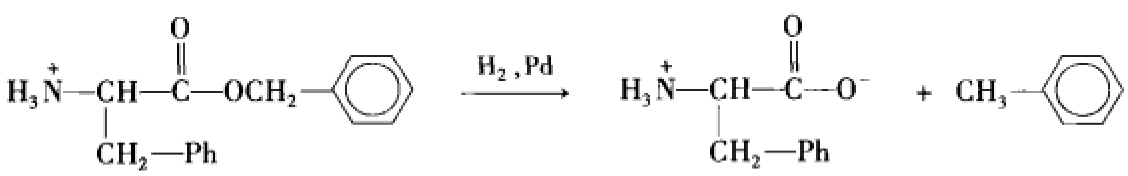
proline(脯氨酸) proline benzyl ester(脯氨酸苄酯) (90%)

Esters of amino acids are often used as protected derivatives to prevent the carboxyl group from reacting in some undesired manner. Methyl, ethyl, and benzyl esters are the most common protecting groups. Aqueous acid hydrolyzes the ester and regenerates the free amino acid.



phenylalanine ethyl ester (苯丙氨酸乙酯) phenylalanine (苯丙氨酸)

Benzyl esters are particularly useful as protecting groups because they can be removed either by acidic hydrolysis or by neutral **hydrogenolysis** ("breaking apart by addition of hydrogen"). Catalytic hydrogenation cleaves the benzyl ester, converting the benzyl group to toluene and leaving the deprotected amino acid. Although the mechanism of this hydrogenolysis is not well known, it apparently hinges on the ease of formation of benzylic intermediates.



phenylalanine benzyl ester (苯丙氨酸苄酯) phenylalanine (苯丙氨酸) toluene (甲苯)

PROBLEM 25-8

Propose a mechanism for the acid-catalyzed hydrolysis of phenylalanine ethyl ester.

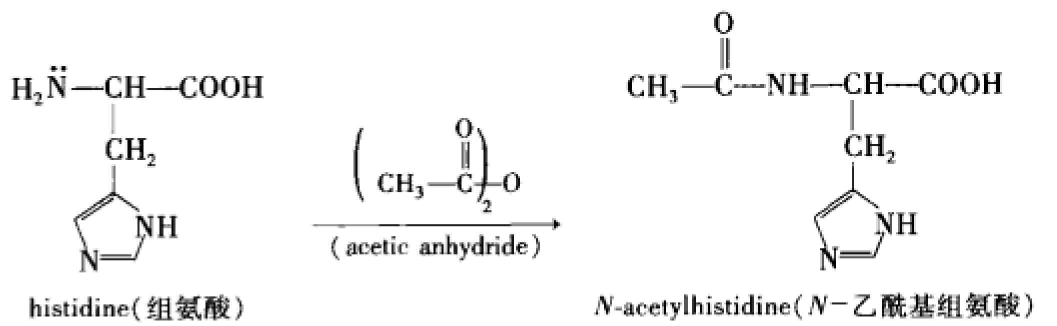
PROBLEM 25-9

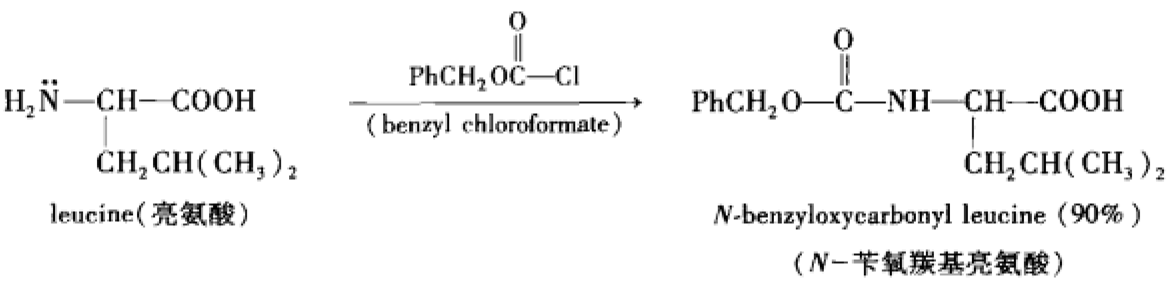
Give equations for the formation and hydrogenolysis of glutamine benzyl ester.

25-7B Acylation of the Amino Group: Formation of Amides

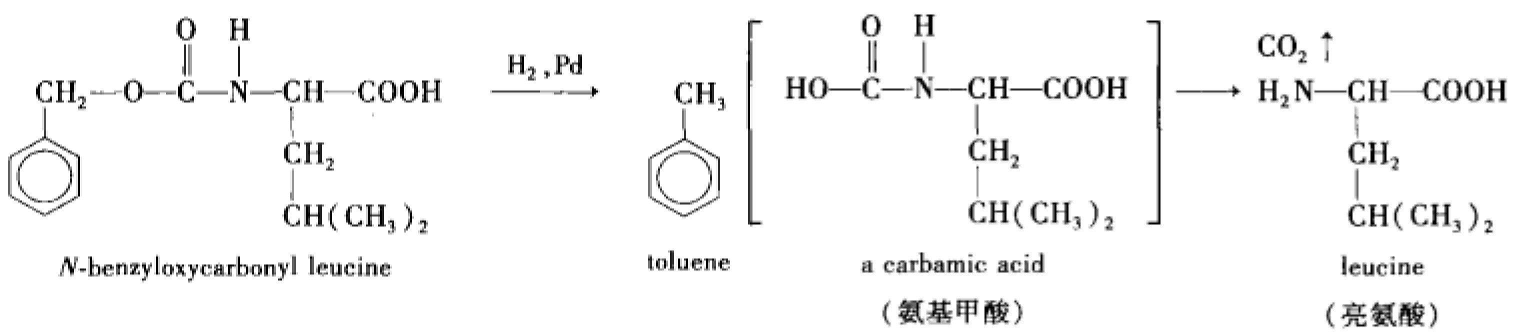
Just as an alcohol esterifies the carboxyl group of an amino acid, an acylating agent converts the amino group to

an amide. Acylation of the amino group is often done to protect it from unwanted nucleophilic reactions. A wide variety of acid chlorides and anhydrides are used for acylation. Benzyl chloroformate acylates the amino group to give a benzyloxycarbonyl derivative, often used as a protecting group in peptide synthesis.





The amino group of the *N*-benzyloxycarbonyl derivative is protected as the amide half of a carbamate ester, which is more easily hydrolyzed than most other amides. In addition, the ester half of this urethane is a benzyl ester that undergoes hydrogenolysis. Catalytic hydrogenolysis of the *N*-benzyloxycarbonyl amino acid gives an unstable carbamic acid that quickly decarboxylates to give the deprotected amino acid.



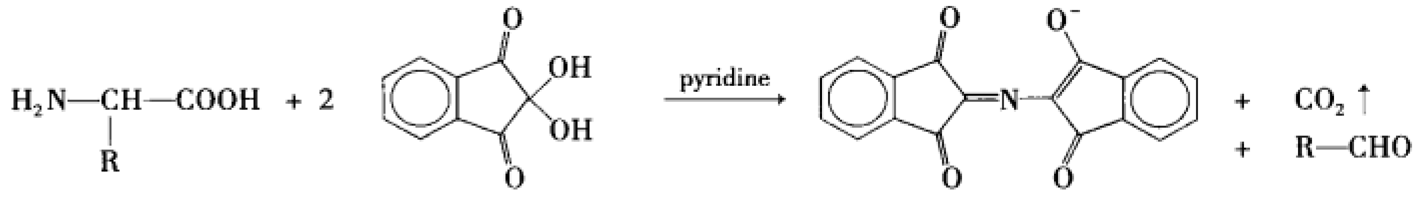
PROBLEM 25-10

Give equations for the formation and hydrogenolysis of *N*-benzyloxycarbonyl methionine.

25-7C Reaction with Ninhydrin

Ninhydrin is a common reagent for visualizing spots or bands of amino acids that have been separated by chromatography or electrophoresis. When ninhydrin reacts with an amino acid, one of the products is a deep violet, resonance-stabilized anion called *Ruhemann's purple*. Ninhydrin produces this same purple dye regardless of the structure of the original amino acid. The side chain of the amino acid is lost as an aldehyde.

Reaction of an amino acid with ninhydrin



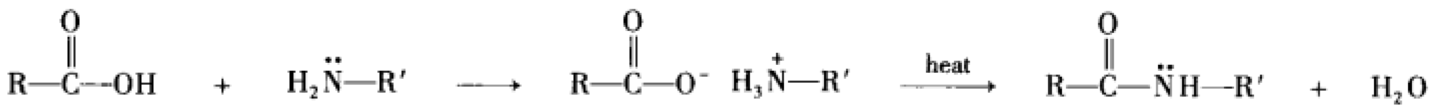
amino acid ninhydrin(水合茚三酮) Ruhemann's purple

The reaction of amino acids with ninhydrin can detect amino acids on a wide variety of substrates. For example, if a kidnapper touches a ransom note with his fingers, the dermal ridges on his fingers leave traces of amino acids from skin secretions. Treatment of the paper with ninhydrin and pyridine causes these secretions to turn purple, forming a visible fingerprint.

25-8 Structure and Nomenclature of Peptides and Proteins

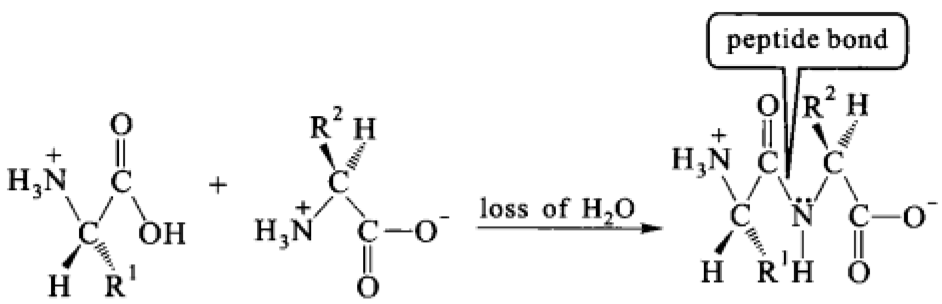
25-8A Peptide Structure

The most important reaction of amino acids is the formation of peptide bonds. Amines and acids can condense, with the loss of water, to form amides. In the laboratory, we might make an amide simply by mixing the acid and the amine, then heating the mixture to drive off water.



acid amine salt amide

Having both an amino group and a carboxyl group, an amino acid is ideally suited to form an amide linkage. Under the proper conditions, the amino group of one molecule condenses with the carboxyl group of another. The product is an amide called a *dipeptide* because it consists of two amino acids. The amide linkage between the amino acids is called a **peptide bond**. Although it has a special name, a peptide bond is just like other amide bonds we have studied.



In this manner, any number of amino acids can be bonded in a continuous chain. A **peptide** is a compound containing two or more amino acids linked by amide bonds between the amino group of each amino acid and the carboxyl group of the neighboring amino acid. Each amino acid unit in the peptide is called a **residue**. A **polypeptide** is a peptide containing many amino acid residues but usually having a molecular weight of less than about 5 000. **Proteins** contain more amino acid units, with molecular weights ranging from about 6 000 to about 40 000 000. The term **oligopeptide** is occasionally used for peptides containing about four to ten amino acid residues. Figure 25-5 shows the structure of the nonapeptide bradykinin, a human hormone that helps to control blood pressure.

The end of the peptide with the free amino group ($—NH_3^+$) is called the **N-terminal end** or the **N terminus**, and the end with the free carboxyl group ($—COO^-$) is called the **C-terminal end** or the **C terminus**. Peptide structures are generally drawn with the N terminus at the left and the C terminus at the right, as bradykinin is drawn in Figure 25-5.

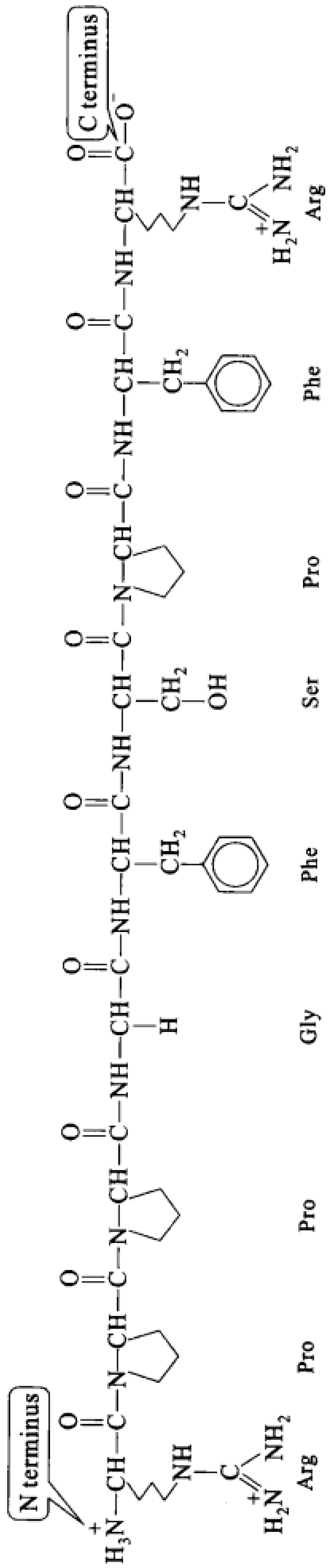
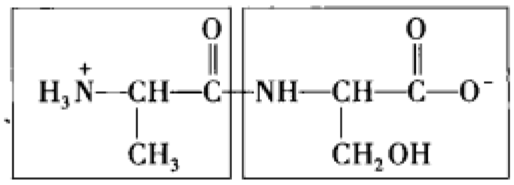


Figure 25-5 The human hormone bradykinin(血管舒缓激肽) is a nonapeptide with a free $—NH_3^+$ at its N terminus and a free $—COO^-$ at its C terminus.

25−8B Peptide Nomenclature

The names of peptides reflect the names of the amino acid residues involved in the amide linkages, beginning at the *N* terminus. All except the last are given the *-yl* suffix of acyl groups. For example, the following dipeptide is named alanylserine. The alanine residue has the *-yl* suffix because it has acylated the nitrogen of serine.



alanyl (丙氨酰)　　serine (丝氨酸)

Ala-Ser

Bradykinin (Figure 25−5) is named as follows (without any spaces):

arginyl prolyl prolyl glycyl phenylalanyl seryl prolyl phenylalanyl arginine
(精氨酰 脯氨酰 脯氨酰 甘氨酰 苯丙氨酰 丝氨酰 脯氨酰 苯丙氨酰 精氨酸)

This is a cumbersome and awkward name. A shorthand system is more convenient, representing each amino acid by its three-letter abbreviation. These abbreviations, given in Table 25−2, are generally the first three letters of the name. Once again, the amino acids are arranged from the N terminus at the left to the C terminus at the right. Bradykinin has the following abbreviated name:

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

Single-letter symbols (also given in Table 25−2) are becoming widely used as well. Using single letters, we symbolize bradykinin by

RPPGFSPFR

PROBLEM 25−11

Draw the complete structures of the following peptides:

(**a**) Thr-Phe-Met　　(**b**) serylarginylglycylphenylalanine　　(**c**) IMQDK　　(**d**) ELVIS

25−8C Disulfide Linkages

Amide linkages (peptide bonds) form the backbone of the amino acid chains we call peptides and proteins. A second kind of covalent bond is possible between any cysteine residues present. Cysteine residues can form **disulfide bridges** (also called **disulfide linkages**) which can join two chains or link a single chain into a ring.

Mild oxidation joins two molecules of a thiol into a disulfide, forming a disulfide linkage between the two thiol molecules. This reaction is reversible, and a mild reduction cleaves the disulfide.

$$\underset{\text{two molecules of thiol}}{R{-}SH + HS{-}R} \underset{[\text{reduction}]}{\overset{[\text{oxidation}]}{\rightleftharpoons}} \underset{\text{disulfide}}{R{-}S{-}S{-}R} + H_2O$$

Similarly, two cysteine sulfhydryl (—SH) groups are oxidized to give a disulfidelinked pair of amino acids. This disulfide-linked dimer of cysteine is called *cystine*. Figure 25−6 shows formation of a cystine disulfide bridge linking two peptide chains.

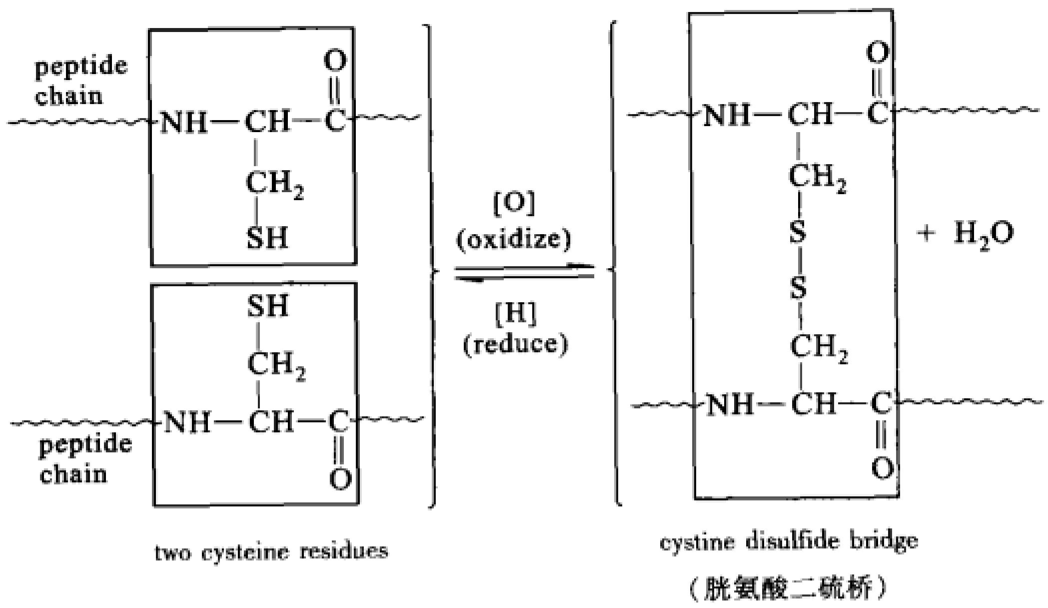


Figure 25-6 Cystine, a dimer of cysteine, results when two cysteine residues undergo oxidation to form a disulfide bridge.

25-9 Peptide Structure Determination

Insulin is a relatively simple protein, yet it is a complicated organic structure. How is it possible to determine the complete structure of a protein with hundreds of amino acid residues and a molecular weight of many thousands? Chemists have developed clever ways to determine the exact sequence of amino acids in a protein. We will consider some of the most common methods.

25-9A Cleavage of Disulfide Linkages

The first step in structure determination is to break all the disulfide bonds, opening any disulfide-linked rings and separating the individual peptide chains. The individual peptide chains are then purified and analyzed separately.

Cystine bridges are easily cleaved by reducing them to the thiol (cysteine) form. These reduced cysteine residues have a tendency to reoxidize and re-form disulfide bridges, however. A more permanent cleavage involves oxidizing the disulfide linkages with peroxyformic acid (Figure 25-7). This oxidation converts the disulfide bridges to sulfonic acid ($—SO_3H$) groups. The oxidized cysteine units are called *cysteic acid* residues.

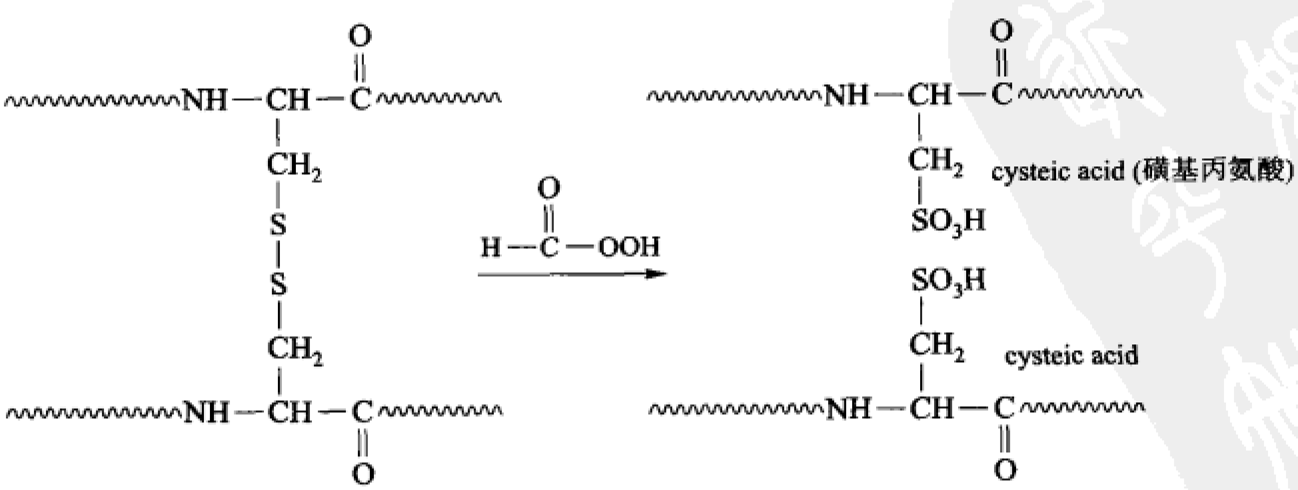


Figure 25-7 Oxidation of a protein by peroxyformic acid.

25-9B Determination of the Amino Acid Composition

Once the disulfide bridges have been broken and the individual peptide chains have been separated and purified, the structure of each chain must be determined. The first step is to determine which amino acids are present and in what proportions. To analyze the amino acid composition, the peptide chain is completely hydrolyzed by boiling it for 24 hours in 6 mol/L HCl. The resulting mixture of amino acids (the *hydrolysate*) is placed on the column of an *amino acid analyzer*.

In the amino acid analyzer, the components of the hydrolysate are dissolved in an aqueous buffer solution and separated by passing them down an ion-exchange column. The solution emerging from the column is mixed with ninhydrin, which reacts with amino acids to give the purple ninhydrin color. The absorption of light is recorded and printed out as a function of time.

The time required for each amino acid to pass through the column (its *retention time*) depends on how strongly that amino acid interacts with the ion-exchange resin. The retention time of each amino acid is known from standardization with pure amino acids. The amino acids present in the sample are identified by comparing their retention times with the known values. The area under each peak is nearly proportional to the amount of the amino acid producing that peak, so we can determine the relative amounts of amino acids present.

Figure 25-8 shows a standard trace of an equimolar mixture of amino acids, followed by the trace produced by the hydrolysate from human bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg).

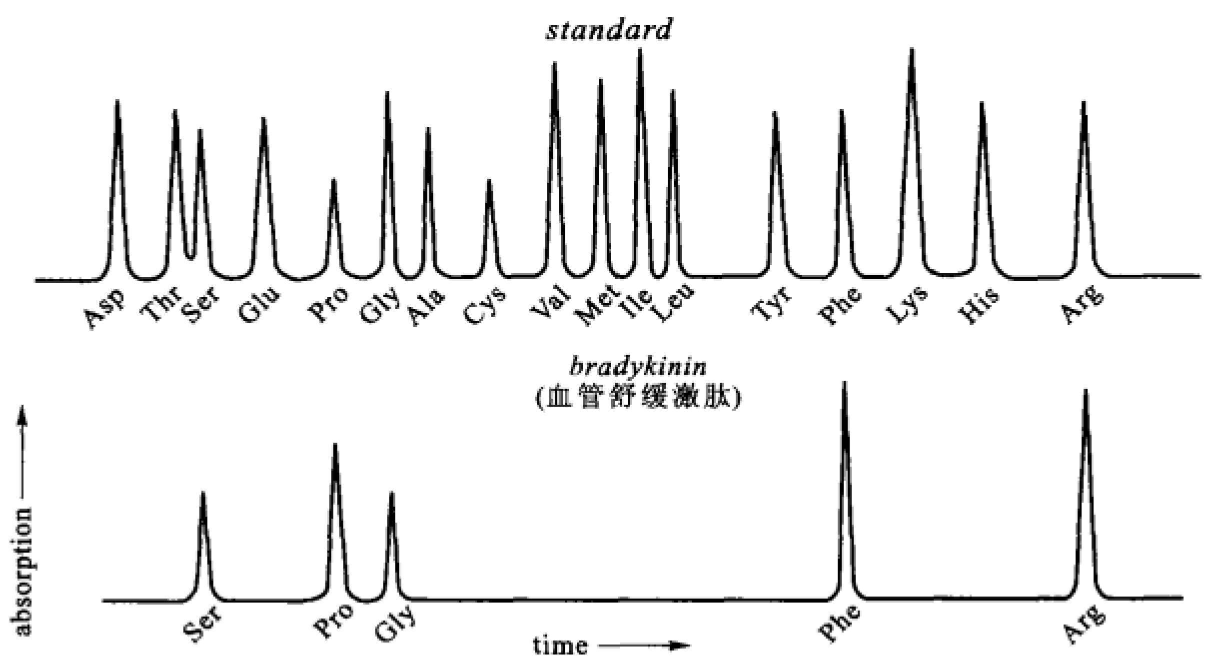


Figure 25-8 Use of an amino acid analyzer to determine the composition of human bradykinin. The bradykinin peaks for Pro, Arg, and Phe are larger than those in the standard equimolar mixture because bradykinin has three Pro residues, two Arg residues, and two Phe residues.

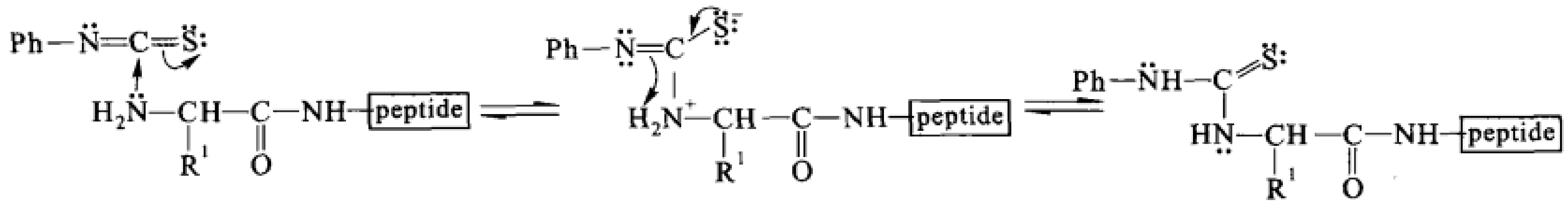
Sequencing the Peptide: Terminal Residue Analysis The amino acid analyzer determines the amino acids present in a peptide, but it does not reveal their **sequence**: the order in which they are linked together. The peptide sequence is destroyed in the hydrolysis step. To determine the amino acid sequence, we must cleave just one amino acid from the chain and leave the rest of the chain intact. The cleaved amino acid can be separated and identified, and the process can be repeated on the rest of the chain. The amino acid may be cleaved from either end of the peptide (either the N terminus or the C terminus), and we will consider one method used for each end. This general method for peptide sequencing is called **terminal residue analysis.**

25-9C Sequencing from the N Terminus: The Edman Degradation

The most efficient method for sequencing peptides is the **Edman degradation**. A peptide is treated with phenyl isothiocyanate, followed by acid hydrolysis. The products are the shortened peptide chain and a heterocyclic derivative of the N-terminal amino acid called a *phenylthiohydantoin*.

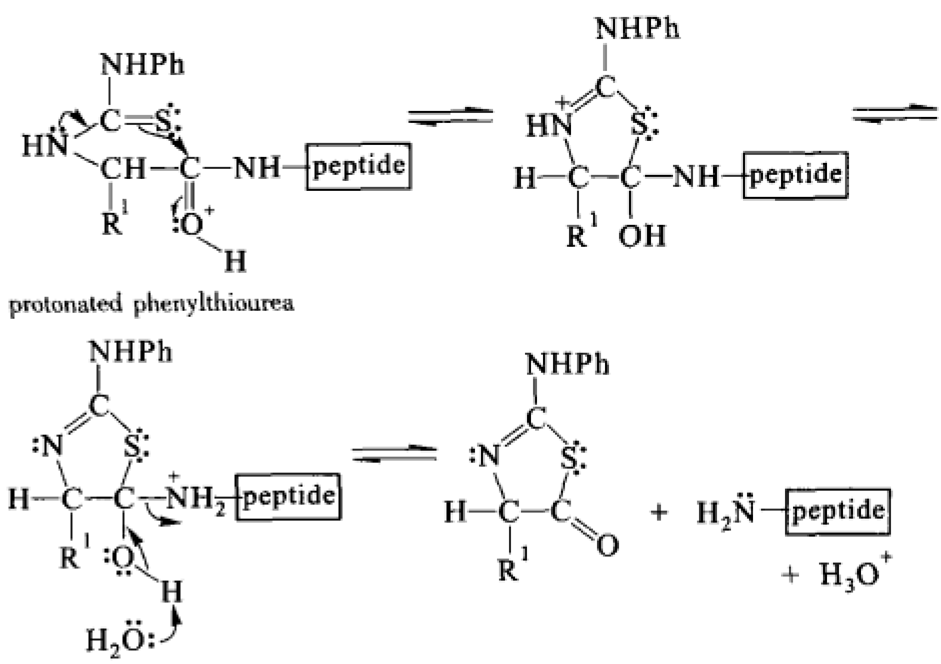
This reaction takes place in three stages. First, the free amino group of the N-terminal amino acid reacts with phenylisothiocyanate to form a phenylthiourea. Second, the phenylthiourea cyclizes to a thiazolinone and expels the shortened peptide chain. Third, the thiazolinone isomerizes to the more stable phenylthiohydantoin.

Step 1: Nucleophilic attack by the free amino group on phenyl isothiocyanate, followed by a proton transfer, gives a phenylthiourea.



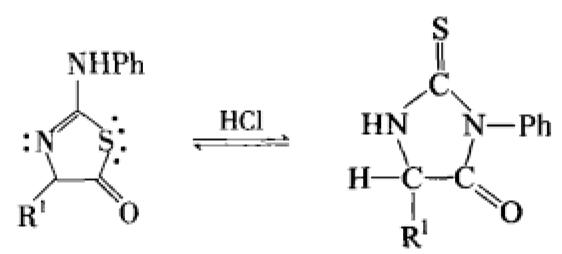
a phenylthiourea (苯硫脲)

Step 2: Treatment with HCl induces cyclization to a thiazolinone and expulsion of the shortened peptide chain.



a thiazolinone (噻唑啉酮)

Step 3: In acid, the thiazolinone isomerizes to the more stable phenylthiohydantoin.

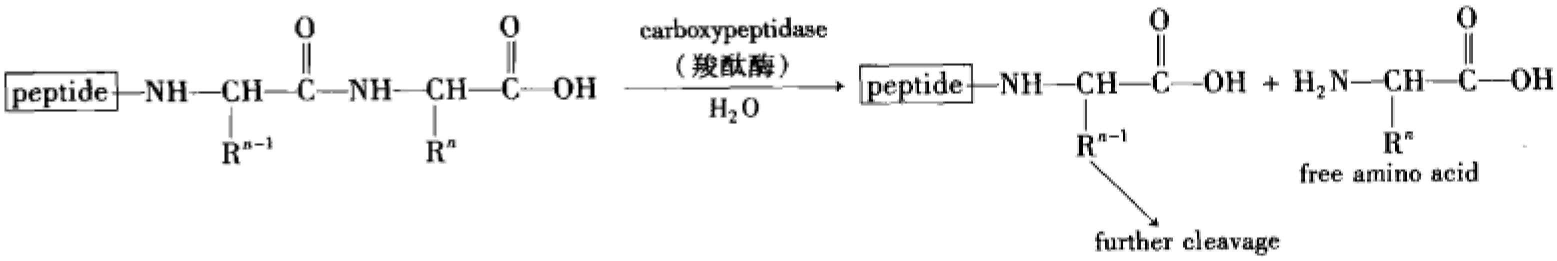


thiazolinone　　a phenylthiohydantoin (苯乙内酰硫脲)

The phenylthiohydantoin derivative is identified by chromatography, by comparing it with phenylthiohydantoin derivatives of the standard amino acids. This gives the identity of the original N-terminal amino acid. The rest of the peptide is cleaved intact, and further Edman degradations are used to identify additional amino acids in the chain. This process is well suited to automation, and several types of automatic sequencers have been developed.

25-9D C-Terminal Residue Analysis

There is no efficient method for sequencing several amino acids of a peptide starting from the C terminus. In many cases, however, the C-terminal amino acid can be identified using the enzyme *carboxypeptidase*, which cleaves the C-terminal peptide bond. The products are the free C-terminal amino acid and a shortened peptide. Further reaction cleaves the second amino acid that has now become the new C terminus of the shortened peptide. Eventually, the entire peptide is hydrolyzed to its individual amino acids.



A peptide is incubated with the carboxypeptidase enzyme, and the appearance of free amino acids is monitored. In theory, the amino acid whose concentration increases first should be the C terminus, and the next amino acid to appear should be the second residue from the end. In practice, different amino acids are cleaved at different rates, making it difficult to determine amino acids past the C terminus and occasionally the second residue in the chain.

25-9E Breaking the Peptide into Shorter Chains: Partial Hydrolysis

Before a large protein can be sequenced, it must be broken into smaller chains, not longer than about 30 amino acids. Each of these shortened chains is sequenced, and then the entire structure of the protein is deduced by fitting the short chains together like pieces of a jigsaw puzzle.

Partial cleavage can be accomplished either by using dilute acid with a short reaction time or by using enzymes, such as *trypsin* and *chymotrypsin*, that break bonds between specific amino acids. The acid-catalyzed cleavage is not very selective, leading to a mixture of short fragments resulting from cleavage at various positions. Enzymes are more selective, giving cleavage at predictable points in the chain.

TRYPSIN: Cleaves the chain at the carboxyl groups of the basic amino acids lysine and arginine.

CHYMOTRYPSIN: Cleaves the chain at the carboxyl groups of the aromatic amino acids phenylalanine, tyrosine, and tryptophan.

Let's use oxytocin as an example to illustrate the use of partial hydrolysis. Oxytocin could be sequenced directly by C-terminal analysis and a series of Edman degradations, but it provides a simple example of how a structure can be pieced together from fragments. Acid-catalyzed partial hydrolysis of oxytocin (after cleavage of the disulfide bridge) gives a mixture that includes the following peptides:

Ile-Gln-Asn-Cys Gln-Asn-Cys-Pro Pro-Leu-Gly·NH_2 Cys-Tyr-Ile-Gln-Asn Cys-Pro-Leu-Gly

When we match the overlapping regions of these fragments, the complete sequence of oxytocin appears:

```
          Ile-Gln-Asn-Cys
              Gln-Asn-Cys-Pro
Cys-Tyr-Ile-Gln-Asn
                  Cys-Pro-Leu-Gly
                      Pro-Leu-Gly·NH2
```

Complete structure

Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly · NH_2

The two Cys residues in oxytocin may be involved in disulfide bridges, either linking two of these peptide units or forming a ring. By measuring the molecular weight of oxytocin, we can show that it contains just one of these peptide units; therefore, the Cys residues must link the molecule in a ring.

PROBLEM 25-12

Show where trypsin and chymotrypsin would cleave the following peptide.

Tyr-Ile-Gln-Arg-Leu-Gly-Phe-Lys-Asn-Trp-Phe-Gly-Ala-Lys-Gly-Gln-Gln · NH_2

PROBLEM 25-13

After treatment with peroxyformic acid, the peptide hormone vasopressin is partially hydrolyzed. The following fragments are recovered. Propose a structure for vasopressin.

Phe-Gln-Asn　　Pro-Arg-Gly · NH_2　　Cys-Tyr-Phe

Asn-Cys-Pro-Arg　　Tyr-Phe-Gln-Asn

25-10 Solution-Phase Peptide Synthesis

25-10A Introduction

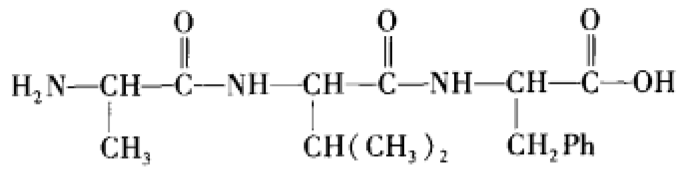
Total synthesis of peptides is rarely an economical method for their commercial production. Important peptides are usually derived from biological sources. For example, insulin for diabetics was originally taken from pork pancreas. Now, recombinant DNA techniques are improving the quality and availability of peptide pharmaceuticals. It is possible to extract the piece of DNA that contains the code for a particular protein, insert it into a bacterium, and induce the bacterium to produce the protein. Strains of *Escherichia coli* have been developed to produce human insulin that avoids dangerous reactions in people who are allergic to pork products.

Laboratory peptide synthesis is still an important area of chemistry, however. When the structure of a new peptide is determined, a synthesis is usually attempted. The purpose of the synthesis is twofold: If the synthetic material is the same as the natural material, it proves that the proposed structure is correct; and the synthesis provides a larger amount of the material for further biological testing. Also, synthetic peptides can be made with altered amino acid sequences to compare their biological activity with the natural peptides. These comparisons can point out the critical areas of the peptide, which may suggest causes and treatments for genetic diseases involving similar abnormal peptides.

Chemists have developed many ways of synthesizing peptides, falling into two major groups. The classical *solution-phase method* involves adding reagents to solutions of growing peptide chains and purifying the products as needed. The *solid-phase method* involves adding reagents to growing peptide chains bonded to solid polymer particles. The solid-phase method has an advantage because spent reagents and impurities are easily washed from the solid particles holding the peptide. Many different reagents and procedures are available for each of these methods, but we will consider only one set of reagents for the solution-phase method and one set for the solid-phase method. The general principles are the same regardless of the specific reagents.

25-10B Solution-Phase Method

Consider the structure of alanylvalylphenylalanine, a simple tripeptide:



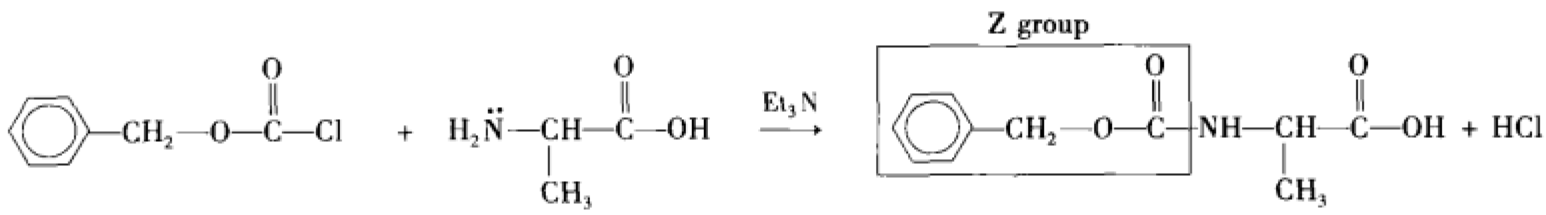
alanyl (丙氨酰) valyl (缬氨酰) phenylalanine (苯丙氨酸)

Ala-Val-Phe

Solution-phase peptide synthesis begins at the N terminus and ends at the C terminus, or left to right as we draw the peptide. The first major step is to couple the carboxyl group of alanine to the amino group of valine. This cannot be done simply by activating the carboxyl group of alanine and adding valine. If we activated the carboxyl group of alanine, it would react with another molecule of alanine.

To prevent side reactions, the amino group of alanine must be protected to make it nonnucleophilic. Treating the free amino acid with benzyl chloroformate (also called *benzyloxycarbonyl chloride*) forms a urethane, or carbamate ester, that is easily removed at the end of the synthesis. This protecting group has been used for many years, and it has acquired several names. It is called the *benzyloxycarbonyl group*, the *carbobenzoxy group* (Cbz), or simply the *Z group* (abbreviated Z).

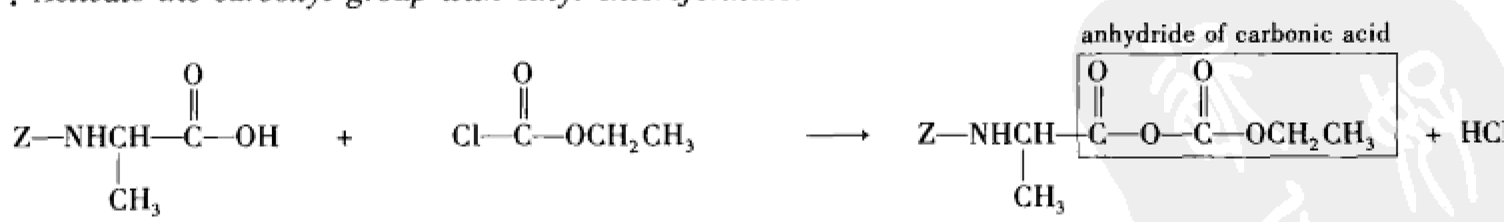
***Preliminary step*:** Protect the amino group with Z.



benzyl chloroformate (氯甲酸苄酯) Z-Cl; alanine (丙氨酸) Ala; benzyloxycarbonyl alanine [苄氧羰基(简写符号Z)丙氨酸] Z-Ala

The amino group in Z-Ala is protected as the nonnucleophilic amide half of a carbamate ester. The carboxyl group can be activated without reacting with the protected amino group. In the solution-phase synthesis, the carboxyl group is activated by treatment with ethyl chloroformate. The product is a mixed anhydride of the amino acid and carbonic acid. It is strongly activated toward nucleophilic attack.

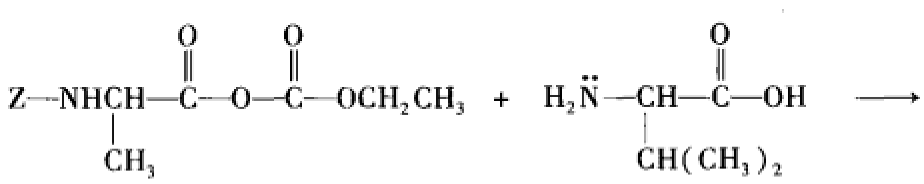
Step 1: Activate the carboxyl group with ethyl chloroformate.



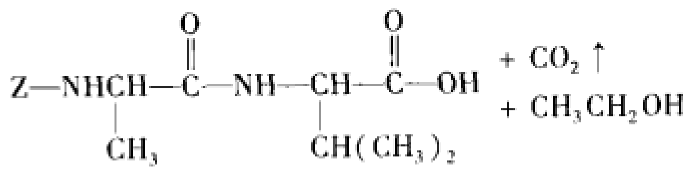
protected alanine; ethyl chloroformate(氯甲酸乙酯); mixed anhydride

When the second amino acid (valine) is added to the protected, activated alanine, the nucleophilic amino group of valine attacks the activated carbonyl of alanine, displacing the anhydride and forming a peptide bond. (Some procedures use an ester of the new amino acid to avoid competing reactions from its carboxylate group.)

Step 2: Form an amide bond to couple the next amino acid.



protected, activated alanine; valine(缬氨酸)



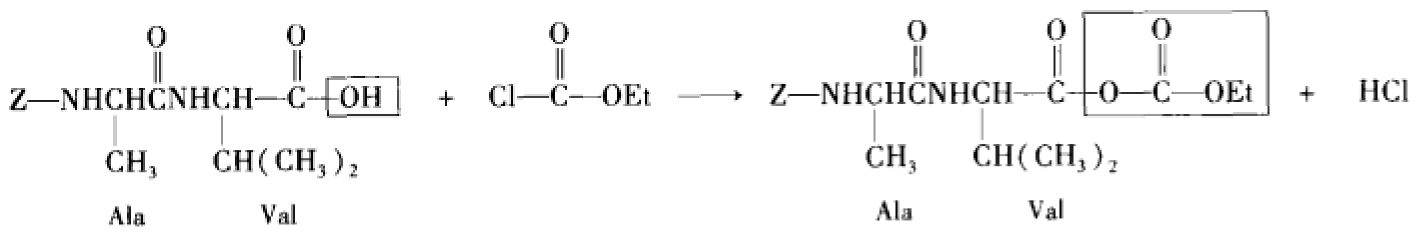
Z-Ala-Val

PROBLEM 25-14

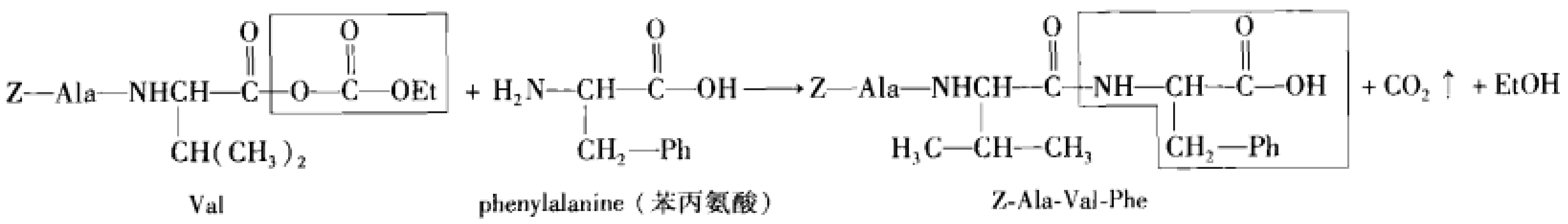
Give complete mechanisms for the formation of Z-Ala, its activation by ethyl chloroformate, and the coupling with valine.

At this point, we have the N-protected dipeptide Z-Ala-Val. Phenylalanine must be added to the C terminus to complete the Ala-Val-Phe tripeptide. Activation of the valine carboxyl group, followed by addition of phenylalanine, gives the protected tripeptide.

Step 1: Activate the carboxyl group with ethyl chloroformate.



Step 2: Form an amide bond to couple the next amino acid.

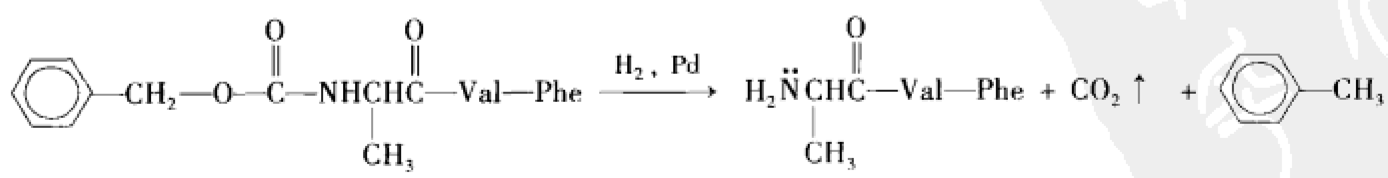


To make a larger peptide, repeat these two steps for the addition of each amino acid residue:

1. Activate the C terminus of the growing peptide by reaction with ethyl chloroformate.
2. Couple the next amino acid.

The final step in the solution-phase synthesis is to deprotect the N terminus of the completed peptide. The N-terminal amide bond must be cleaved without breaking any of the peptide bonds in the product. Fortunately, the benzyloxycarbonyl group is partly an amide and partly a benzyl ester, and hydrogenolysis of the benzyl ester takes place under mild conditions that do not cleave the peptide bonds. This mild cleavage is the reason for using the benzyloxycarbonyl group (as opposed to some other acyl group) to protect the N terminus.

***Final step*:** Remove the protecting group.



The solution-phase method works well for small peptides, and many peptides have been synthesized by this process. A large number of chemical reactions and purifications are required even for a small peptide, however. Although the individual yields are excellent, with a large peptide, the overall yield becomes so small as to be unusable, and several months (or years) are required to complete so many steps. The large amounts of time

required and the low overall yields are due largely to the purification steps. For larger peptides and proteins, solid-phase peptide synthesis is usually preferred.

PROBLEM 25-15

Show how you would synthesize Ala-Val-Phe-Gly-Leu starting with Z-Ala-Val-Phe.

PROBLEM 25-16

Show how the solution-phase synthesis would be used to synthesize Ile-Gly-Asn.

25-11 Solid-Phase Peptide Synthesis

In 1962, Robert Bruce Merrifield of Rockefeller University developed a method for synthesizing peptides without having to purify the intermediates. He did this by attaching the growing peptide chains to solid polystyrene beads. After each amino acid is added, the excess reagents are washed away by rinsing the beads with solvent. This ingenious method lends itself to automation, and Merrifield built a machine that can add several amino acid units while running unattended. Using this machine, Merrifield synthesized ribonuclease (124 amino acids) in just six weeks, obtaining an overall yield of 17%. Merrifield's work in solid-phase peptide synthesis won the Nobel Prize in chemistry in 1984.

25-11A The Individual Reactions

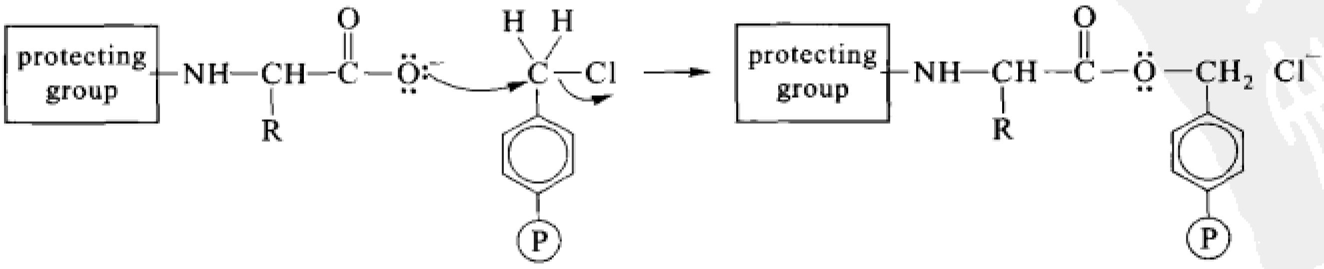
There are three important reactions to consider before we use solid-phase peptide synthesis. We must first learn how an amino acid is attached to the solid support, how and why the amino group is protected, and how peptide bonds are formed.

Attaching the Peptide to the Solid Support The greatest difference between solution-phase and solid-phase peptide synthesis is that solid-phase synthesis is done in the opposite direction: starting with the C terminus and going toward the N terminus, right to left as we write the peptide. The first step is to attach the *last* amino acid (the C terminus) to the solid support.

The solid support is a special polystyrene bead in which some of the aromatic rings have chloromethyl groups. This polymer, often called the *Merrifield resin*, is made by copolymerizing styrene with a few percent of *p*-(chloromethyl) styrene.

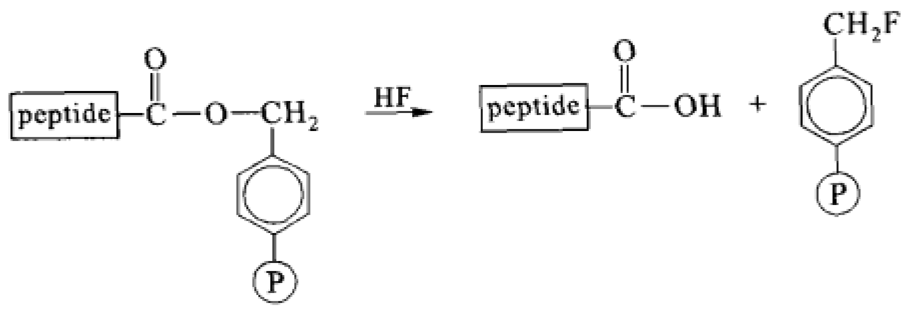
Like other benzyl halides, the chloromethyl groups on the polymer are reactive toward S_N2 attack. The carboxyl group of an N-protected amino acid displaces chloride, giving an amino acid ester of the polymer. In effect, the polymer serves as the alcohol part of an ester protecting group for the carboxyl end of the C-terminal amino acid.

Attachment of the C-terminal amino acid



Once the C-terminal amino acid is fixed to the polymer, the chain is built on the amino group of this amino acid. At the completion of the synthesis, the ester bond to the polymer is cleaved by anhydrous HF. Because this is an ester bond, it is more easily cleaved than the amide bonds of the peptide.

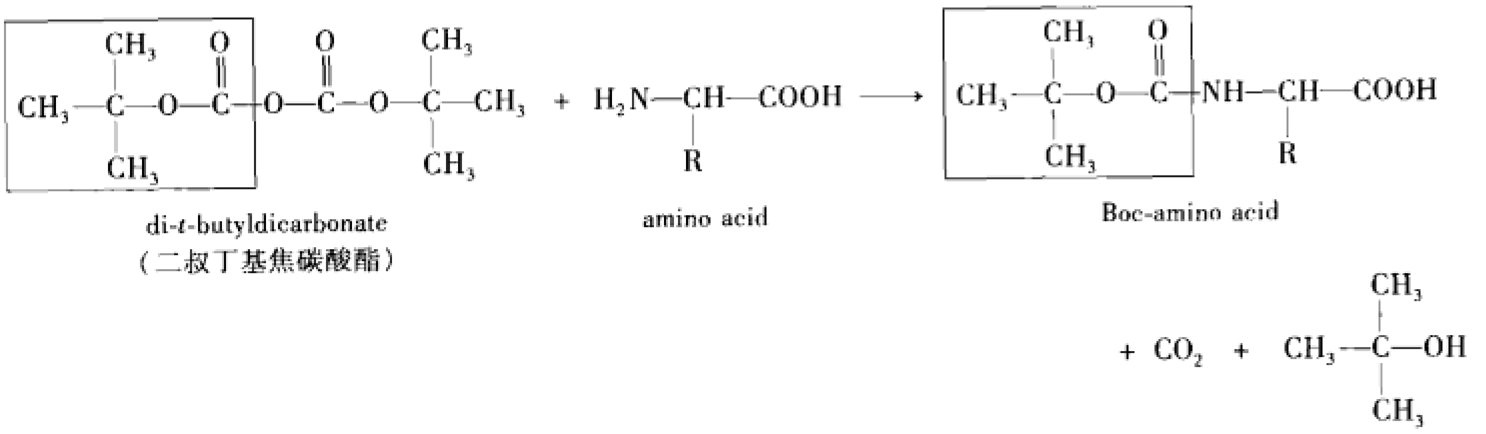
Cleavage of the finished peptide



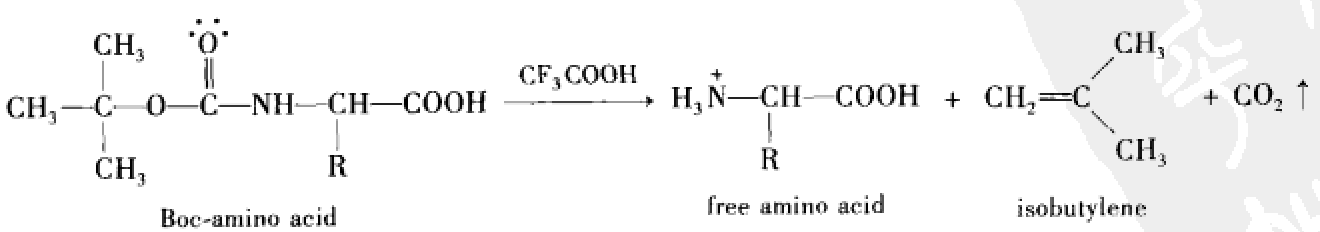
Use of the *t*-Butyloxycarbonyl (Boc) Protecting Group The benzyloxycarbonyl group (the Z group) cannot be used with the solid-phase process because the Z group is removed by hydrogenolysis in contact with a solid catalyst. A polymer-bound peptide cannot achieve the intimate contact with a solid catalyst required for hydrogenolysis. The N-protecting group used in the Merrifield procedure is the *t*-butyloxycarbonyl group, abbreviated Boc or *t*-Boc. The Boc group is similar to the Z group, except that it has a *t*-butyl group in place of the benzyl group. Like other *t*-butyl esters, the Boc protecting group is easily removed under acidic conditions.

The acid chloride of the Boc group is unstable, so we use the anhydride, di-*t*-butyldicarbonate, to attach the group to the amino acid.

Protection of the amino group as its Boc derivative

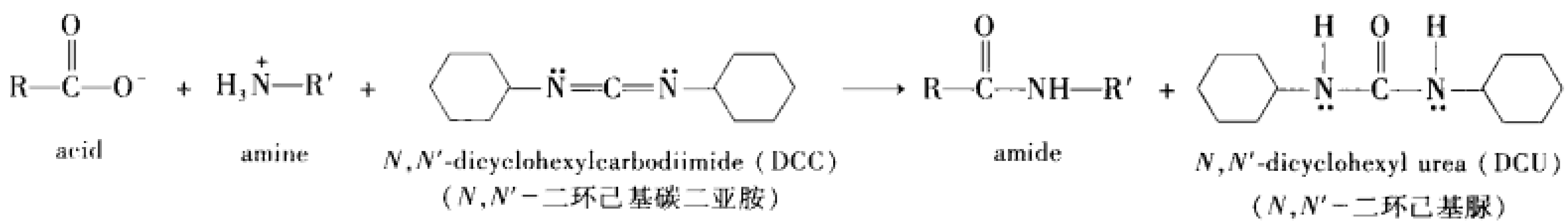


The Boc group is easily cleaved by brief treatment with trifluoroacetic acid (TFA), CF_3COOH. Loss of a relatively stable *t*-butyl cation from the protonated ester gives an unstable carbamic acid. Decarboxylation of the carbamic acid gives the deprotected amino group of the amino acid. Loss of a proton from the *t*-butyl cation gives isobutylene.



Use of DCC as a Peptide Coupling Agent The final reaction needed for the Merrifield procedure is the peptide bond-forming condensation. When a mixture of an amine and an acid is treated with *N*,*N*′-dicyclohexylcarbodiimide (abbreviated DCC), the amine and the acid couple to form an amide. The molecule of water lost in

this condensation converts DCC to N,N'-dicyclohexyl urea (DCU).



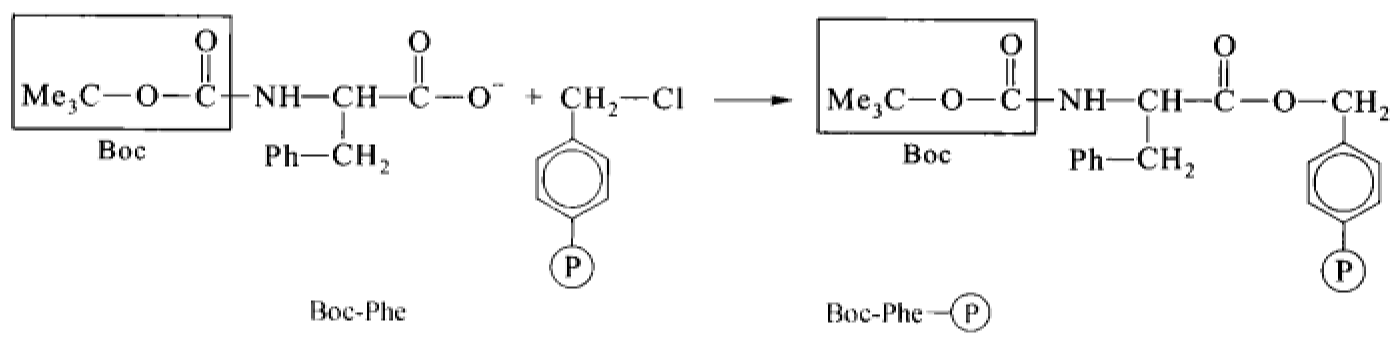
Now we consider an example to illustrate how these procedures are combined in the Merrifield solid-phase peptide synthesis.

25-11B An Example of Solid-Phase Peptide Synthesis

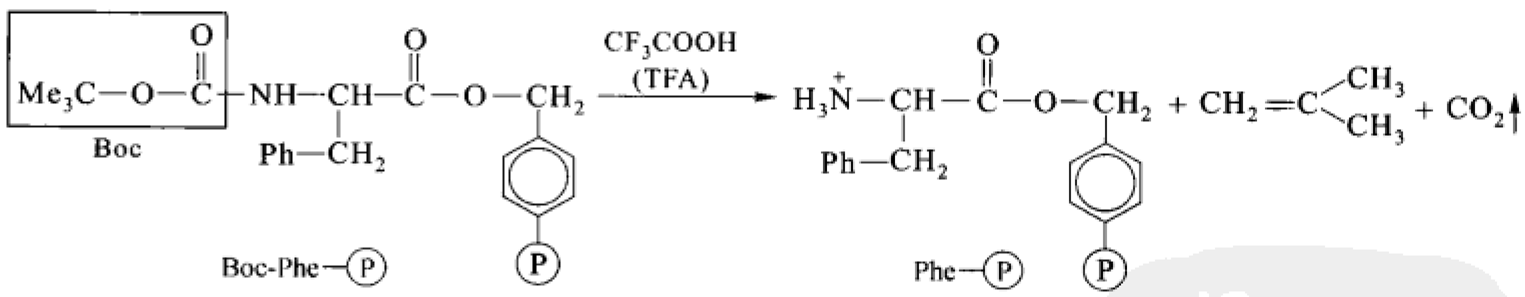
For easy comparison of the solution-phase and solid-phase methods, we will consider the synthesis of the same tripeptide we made using the solution-phase method.

Ala-Val-Phe

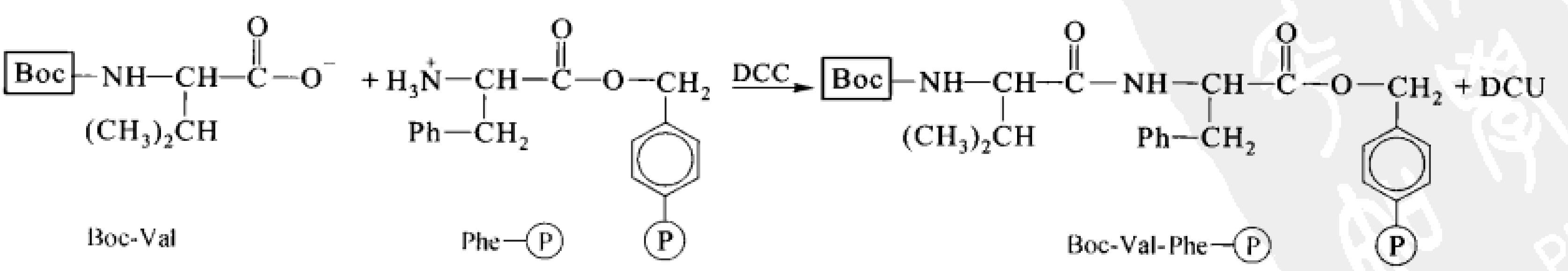
The solid-phase synthesis is carried out in the direction opposite that of the solution-phase synthesis. The first step is attachment of the N-protected C-terminal amino acid (Boc-phenylalanine) to the polymer.



Trifluoroacetic acid (TFA) cleaves the Boc protecting group of phenylalanine so that its amino group can be coupled with the next amino acid.

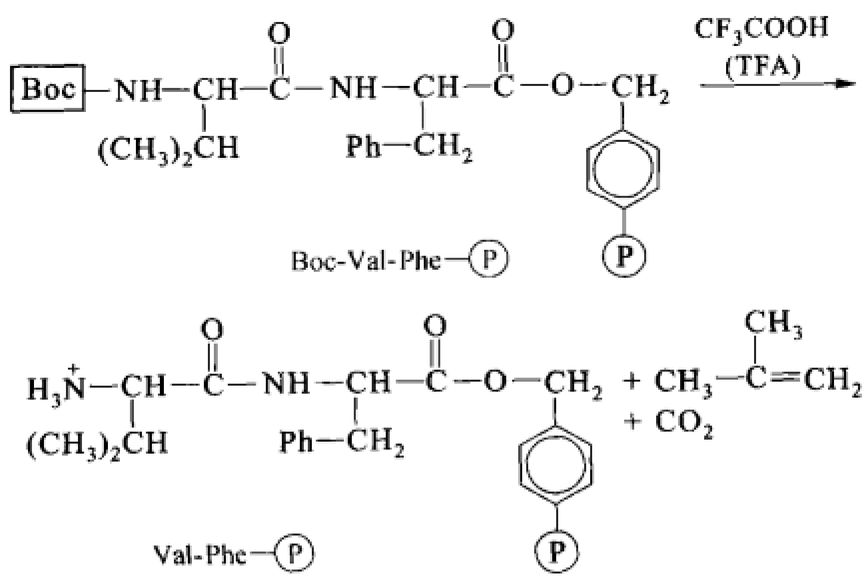


The second amino acid (valine) is added in its N-protected Boc form so that it cannot couple with itself. Addition of DCC couples the valine carboxyl group with the free $—NH_2$ group of phenylalanine.

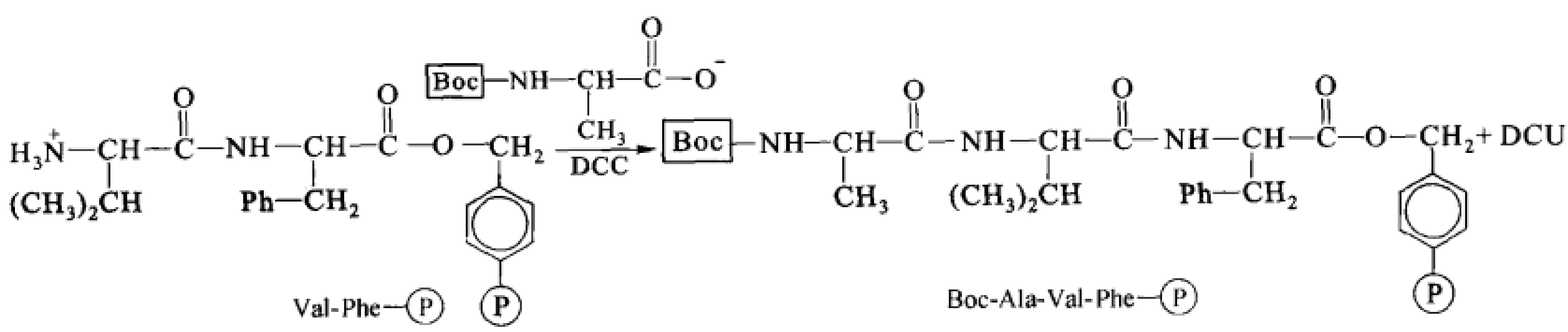


To couple the final amino acid (alanine), the chain is first deprotected by treatment with trifluoroacetic acid. Then the N-protected Boc-alanine and DCC are added.

Step 1: Deprotection



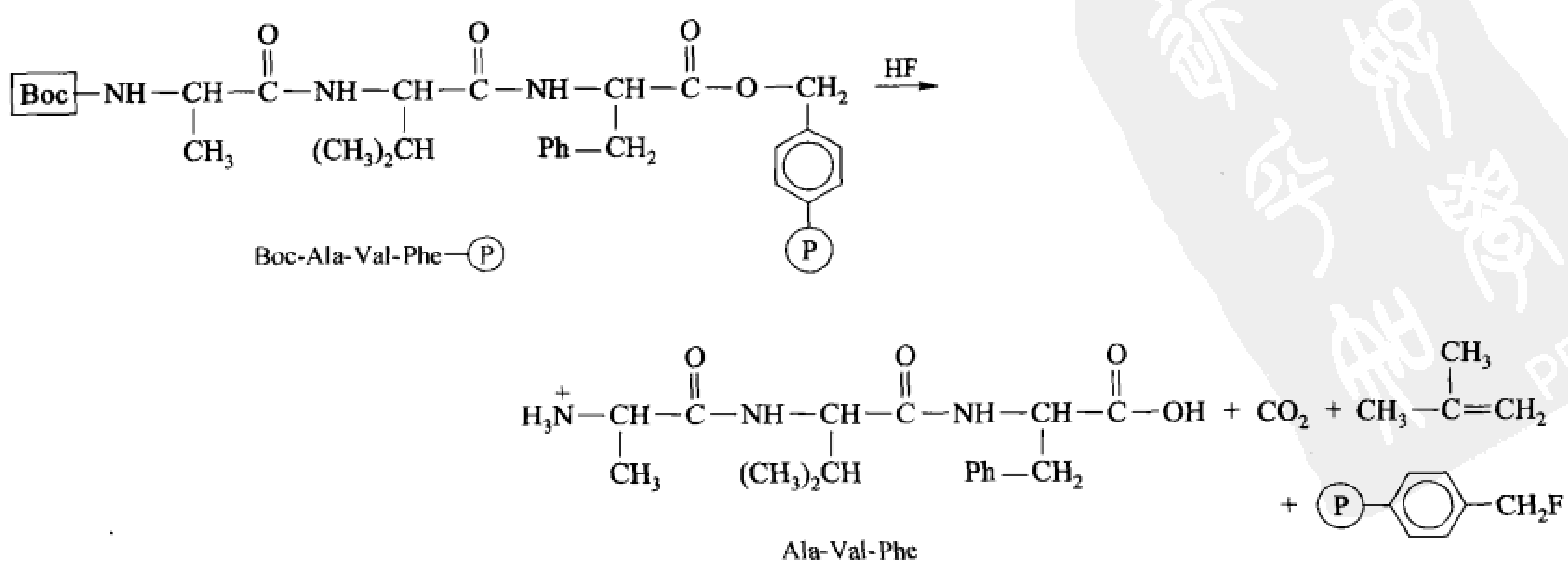
Step 2: Coupling



If we were making a longer peptide, the addition of each subsequent amino acid would require the repetition of two steps:

1. Use trifluoroacetic acid to deprotect the amino group at the end of the growing chain.
2. Add the next Boc-amino acid, using DCC as a coupling agent.

Once the peptide is completed, the final Boc protecting group must be removed, and the peptide must be cleaved from the polymer. Anhydrous HF cleaves the ester linkage that bonds the peptide to the polymer, and it also removes the Boc protecting group. In our example, the following reaction occurs:



PROBLEM 25-17

Show how you would synthesize Leu-Gly-Ala-Val-Phe starting with Boc-Ala-Val-Phe—Ⓟ.

PROBLEM 25-18

Show how solid-phase peptide synthesis would be used to make Ile-Gly-Asn.

25-12 Classification of Proteins

Proteins may be classified according to their chemical composition, their shape, or their function. Protein composition and function are treated in detail in a biochemistry course. For now, we briefly survey the types of proteins and their general classifications.

Proteins are grouped into *simple* and *conjugated* proteins according to their chemical composition. **Simple proteins** are those that hydrolyze to give only amino acids. All the protein structures we have considered so far are simple proteins. Examples are insulin, ribonuclease, oxytocin, and bradykinin. **Conjugated proteins** are bonded to a nonprotein **prosthetic group** such as a sugar, a nucleic acid, a lipid, or some other group. Table 25-3 lists some examples of conjugated proteins.

TABLE 25-3 Classes of Conjugated Proteins

Class	Prosthetic Group	Examples
glycoproteins（糖蛋白）	carbohydrates（糖类）	γ-globulin, interferon（γ-球蛋白,干扰素）
nucleoproteins（核蛋白）	nucleic acids（核酸）	ribosomes, viruses（核蛋白体,病毒）
lipoproteins（脂蛋白）	fats, cholesterol（脂肪,胆固醇）	high-density lipoprotein（高密脂蛋白）
metalloproteins（金属蛋白）	a complexed metal（金属络合）	hemoglobin, cytochromes（血红蛋白,细胞色素）

Proteins are classified as *fibrous* or *globular* depending on whether they form long filaments or coil up on themselves. **Fibrous proteins** are stringy, tough, and usually insoluble in water. They function primarily as structural parts of the organism. Examples of fibrous proteins are α-keratin in hooves and fingernails, and collagen in tendons. **Globular proteins** are folded into roughly spherical shapes. They usually function as enzymes, hormones, or transport proteins. **Enzymes** are protein-containing biological catalysts; an example is ribonuclease, which cleaves RNA. Hormones help to regulate processes in the body; an example is insulin, which regulates glucose levels in the blood and its uptake by cells. Transport proteins bind to specific molecules and transport them through cell membrane or in the blood; an example is hemoglobin, which transports oxygen in the blood from the lungs to the tissues.

25-13 Levels of Protein Structure

25-13A Primary Structure

Up to now, we have discussed the *primary structure* of proteins. The **primary structure** is the covalently bonded structure of the molecule. This definition includes the sequence of amino acids, together with any disulfide bridges. All the properties of the protein are determined, directly or indirectly, by the primary structure. Any folding,

hydrogen bonding, or catalytic activity depends on the proper primary structure.

25−13B Secondary Structure

Although we often think of peptide chains as linear structures, they tend to form orderly hydrogen-bonded arrangements. In particular, the carbonyl oxygen atoms form hydrogen bonds with the amide (N—H) hydrogens. This tendency leads to orderly patterns of hydrogen bonding: the **α helix** and the **pleated sheet**. These hydrogenbonded arrangements, if present, are called the **secondary structure** of the protein.

When a peptide chain winds into a helical coil, each carbonyl oxygen can hydrogen-bond with an N—H hydrogen on the next turn of the coil. Many proteins wind into an α helix (a helix that looks like the thread on a right-handed screw) with the side chains positioned on the outside of the helix. For example, the fibrous protein α keratin is arranged in the α -helical structure, and most globular proteins contain segments of α helix. Figure 25−9 shows the α -helical arrangement.

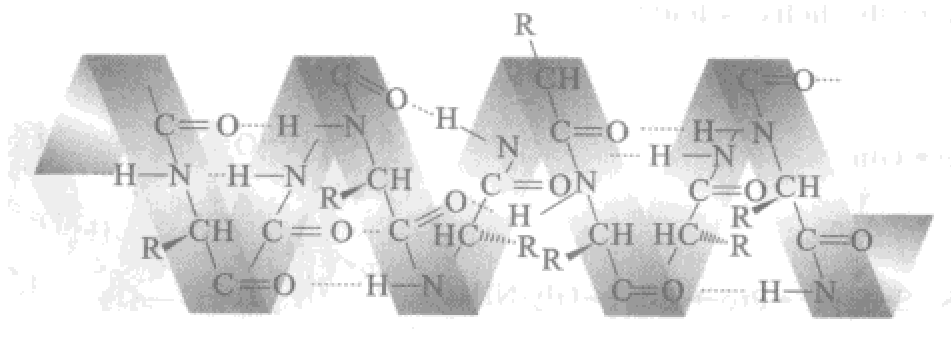


Figure 25−9 The α helical arrangement.

Segments of peptides can also form orderly arrangements of hydrogen bonds by lining up side-by-side. In this arrangement, each carbonyl group on one chain forms a hydrogen bond with an N—H hydrogen on an adjacent chain. This arrangement may involve many peptide molecules lined up side-by-side, resulting in a two-dimensional *sheet*. The bond angles between amino acid units are such that the sheet is *pleated* (creased), with the amino acid side chains arranged on alternating sides of the sheet. Silk fibroin, the principal fibrous protein in the silks of insects and arachnids, has a pleated sheet secondary structure. Figure 25−10 shows the pleated sheet structure.

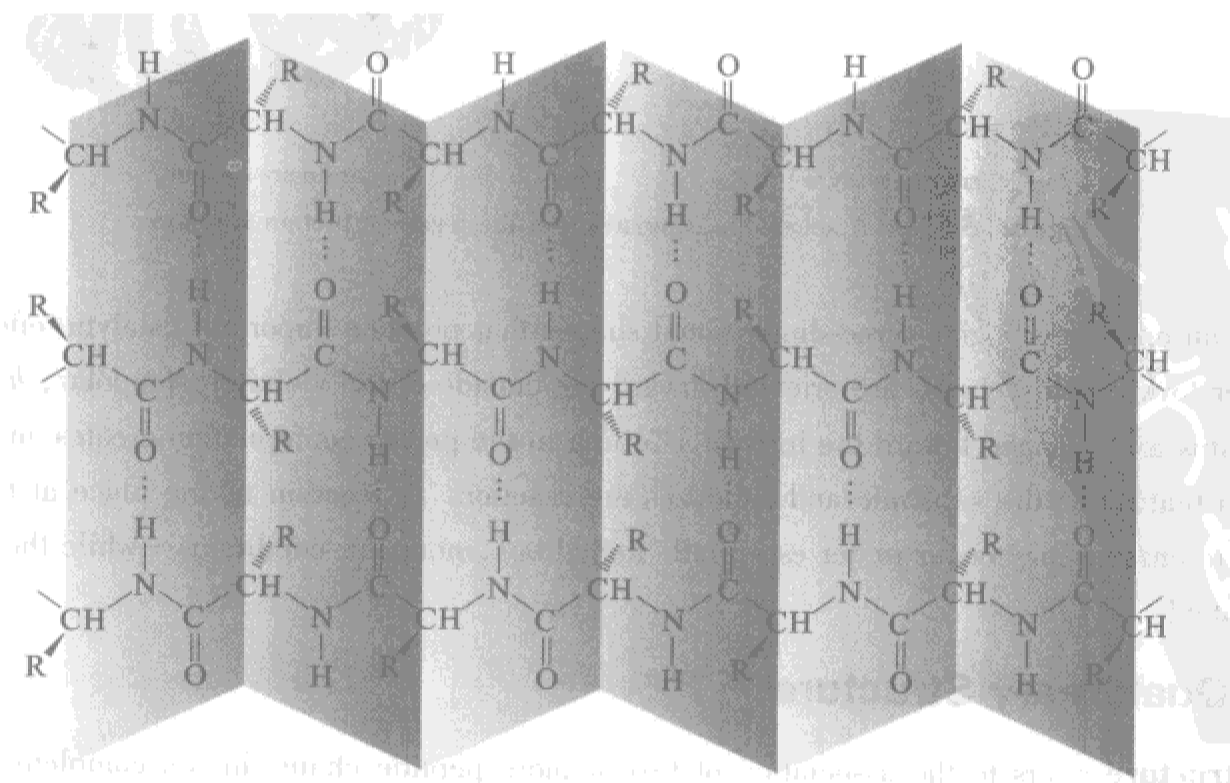


Figure 25−10 The pleated sheet arrangement.

A protein may or may not have the same secondary structure throughout its length. Some parts may be curled into an α helix, while other parts are lined up in a pleated sheet. Parts of the chain may have no orderly secondary structure at all. Such a structureless region is called a **random coil**. Most globular proteins, for example, contain segments of α helix or pleated sheet separated by kinks of random coil, allowing the molecule to fold into its globular shape.

25-13C Tertiary Structure

The **tertiary structure** of a protein is its complete three-dimensional conformation. Think of the secondary structure as a spatial pattern in a local region of the molecule. Parts of the protein may have the α-helical structure, while other parts may have the pleated-sheet structure, and still other parts may be random coils. The tertiary structure includes all the secondary structure and all the kinks and folds in between. The tertiary structure of a typical globular protein is represented in Figure 25-11, which includes segments of α helix with segments of random coil at the points where the helix is folded.

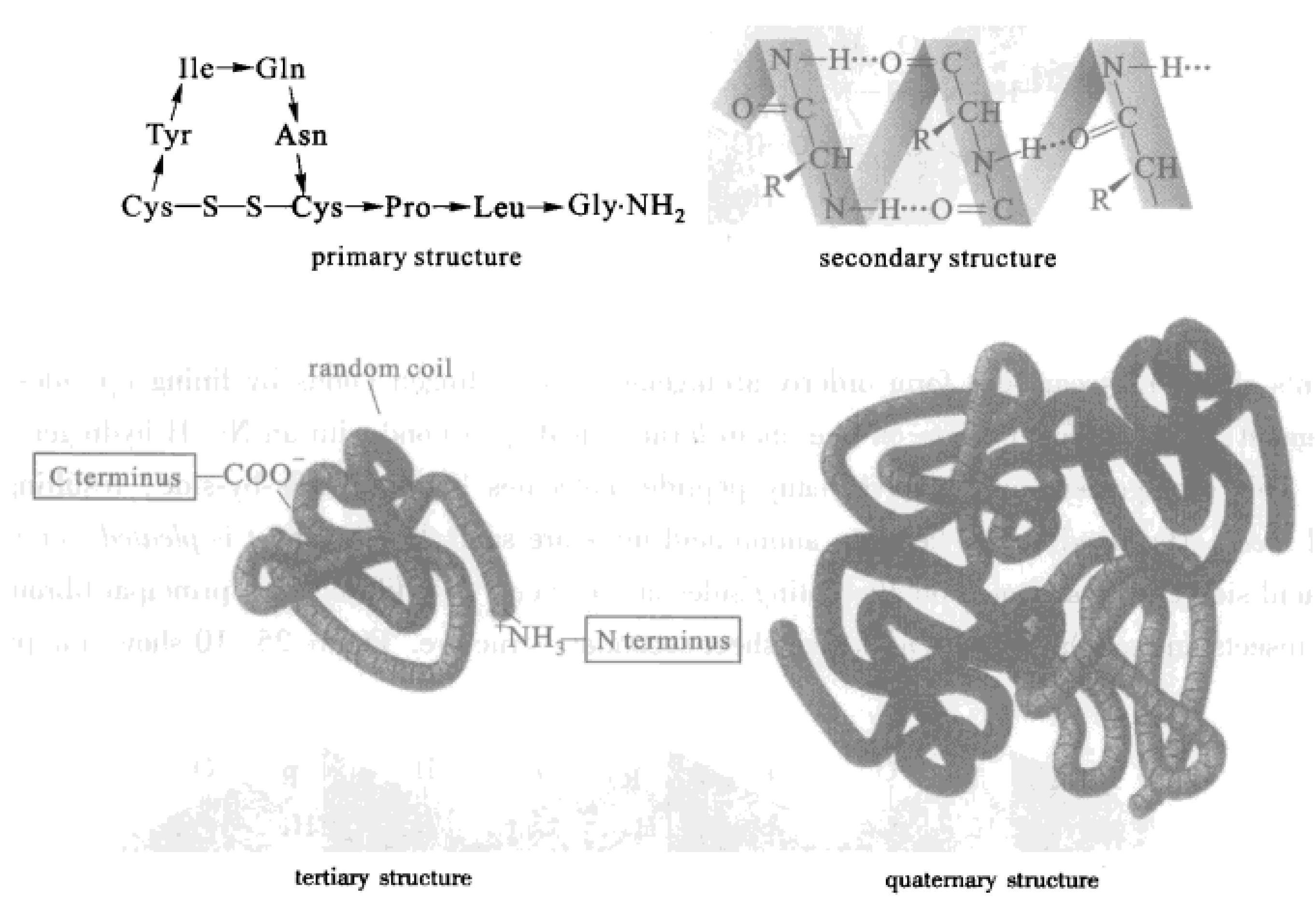


Figure 25-11 A schematic comparison of the levels of protein structure.

Coiling of an enzyme can give three-dimensional shapes that produce important catalytic effects. Polar, *hydrophilic* (water-loving) side chains are oriented toward the outside of the globule. Nonpolar, *hydrophobic* (water-hating) groups are arranged toward the interior. Coiling in the proper conformation creates an enzyme's **active site**, the region that binds the substrate and catalyzes the reaction. A reaction taking place at the active site in the interior of an enzyme may occur under essentially anhydrous, nonpolar conditions—while the whole system is dissolved in water!

25-13D Quaternary Structure

Quaternary structure refers to the association of two or more peptide chains in the complete protein. Not all proteins have quaternary structure. The ones that do are those that associate together in their active form. For

example, hemoglobin, the oxygen carrier in mammalian blood, consists of four peptide chains fitted together to form a globular protein. Figure 25 - 11 summarizes the four levels of protein structure.

25 - 14 Protein Denaturation

For a protein to be biologically active, it must have the correct structure at all levels. The sequence of amino acids must be right, with the correct disulfide bridges linking the cysteines on the chains. The secondary and tertiary structures are important, as well. The protein must be folded into its natural conformation, with the appropriate areas of α helix and pleated sheet. For an enzyme, the active site must have the right conformation, with the necessary side-chain functional groups in the correct positions. Conjugated proteins must have the right prosthetic groups, and multichain proteins must have the right combination of individual peptides.

With the exception of the covalent primary structure, all these levels of structure are maintained by weak solvation and hydrogen-bonding forces. Small changes in the environment can cause a chemical or conformational change resulting in **denaturation**: disruption of the normal structure and loss of biological activity. Many factors can cause denaturation, but the most common ones are heat and pH.

The cooking of egg white is an example of protein denaturation by high temperature. Egg white contains soluble globular proteins called *albumins*. When egg white is heated, the albumins unfold and coagulate to produce a solid rubbery mass. Different proteins have different abilities to resist the denaturing effect of heat. Egg albumin is quite sensitive to heat, but bacteria that live in geothermal hot springs have developed proteins that retain their activity in boiling water.

When a protein is subjected to an acidic pH, some of the side-chain carboxyl groups become protonated and lose their ionic charge. Conformational changes result, leading to denaturation. In a basic solution, amino groups become deprotonated, similarly losing their ionic charge, causing conformational changes and denaturation.

Milk turns sour because of the bacterial conversion of carbohydrates to lactic acid. When the pH becomes strongly acidic, soluble proteins in milk are denatured and precipitate. This process is called *curdling*. Some proteins are more resistant to acidic and basic conditions than others. For example, most digestive enzymes such as amylase and trypsin remain active under acidic conditions in the stomach, even at a pH of about 1.

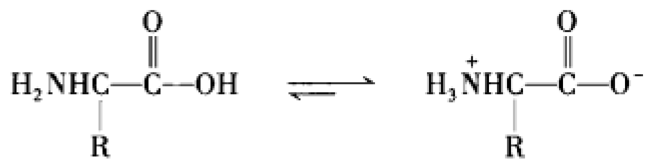
In many cases, denaturation is irreversible. When cooked egg white is cooled, it does not become uncooked. Curdled milk does not uncurdle when it is neutralized. Denaturation may be reversible, however, if the protein has undergone only mild denaturing conditions. For example, a protein can be *salted out* of solution by a high salt concentration, which denatures and precipitates the protein. When the precipitated protein is redissolved in a solution with a lower salt concentration, it usually regains its activity together with its natural conformation.

Summary in Chinese

本 章 概 要

一、氨基酸的结构

羧酸分子中烃基上的氢原子被氨基替代的化合物。自然界中的氨基酸几乎都是 α-氨基酸，构型为 L 型。根据分子中含氨基和羧基的数目不同，可分为中性氨基酸、酸性氨基酸和碱性氨基酸。α-氨基酸中有氨基和羧基，呈现两性，通常是以内盐的形式存在，属偶极离子。即

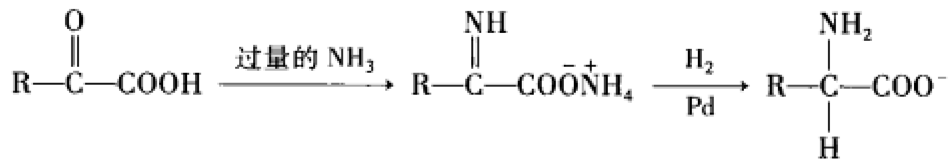


二、氨基酸的物理性质

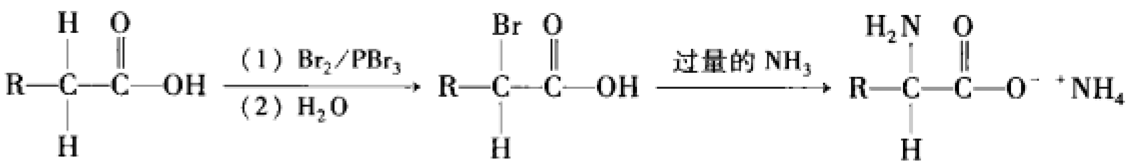
氨基酸的偶极结构使其具有如下特性：熔点高，一般超过 200 ℃；在水中有很好的溶解性；具有比胺和酸大的偶极矩；比羧酸的酸性小，比胺的碱性也小（事实上，起酸性作用的是—N^+H_3 而不是—COOH，起碱性作用的是—COO^- 而不是—NH_2）。

三、氨基酸的制备

1. α－酮酸的还原氨化法（reductive amination of α-ketoacid）：

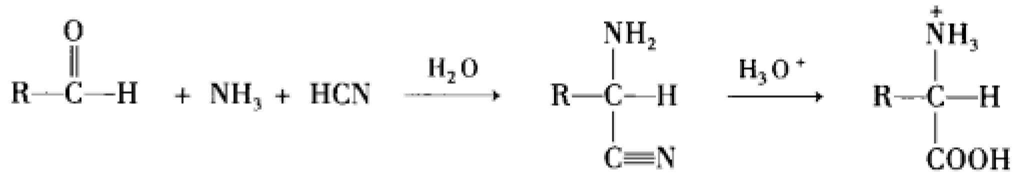


2. α－卤代酸的氨化（amination of an α-haloacid）：

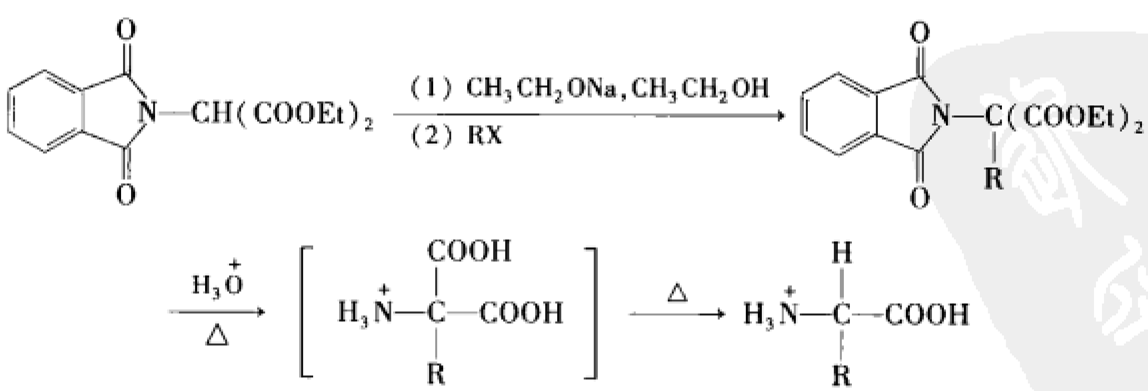


☆ 氨基酸中的氨基比胺的碱性弱，亲核能力弱，反应可控制在一元烷基化阶段。

3. Strecker 合成：



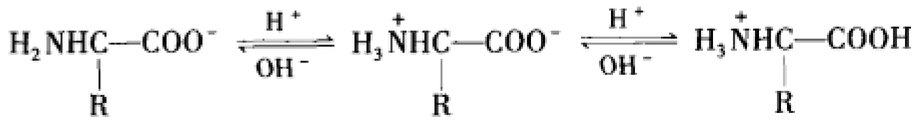
4. Gabriel－丙二酸酯法合成（Gabriel-malonic ester synthesis）：



四、氨基酸的化学性质

氨基酸分子中含有氨基和羧基，所以具有氨基和羧基的性质，同时，官能团之间的相互影响，使其具有一些特性。

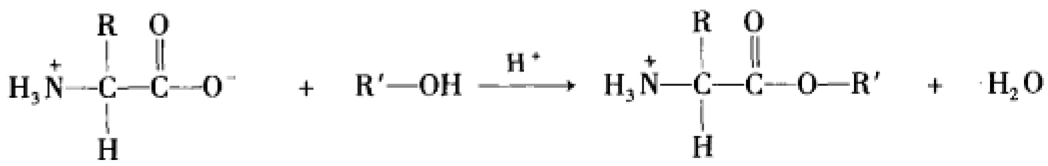
1. 等电点（isoelectric points）：氨基酸在水溶液中存在如下平衡体系，表现出两性离子性质：



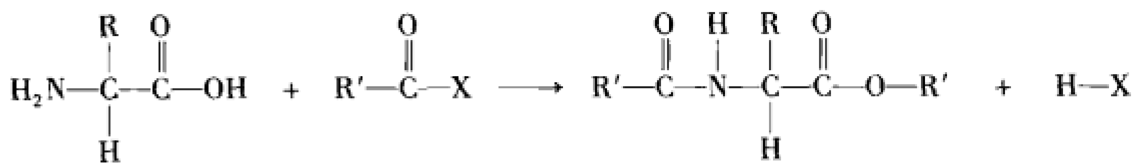
（Ⅰ）负离子　　（Ⅱ）两性离子　　（Ⅲ）正离子

☆ 上述平衡中，若将溶液调至碱性时，该氨基酸主要以（Ⅰ）的形式存在；调至酸性时，以（Ⅲ）的形式存在，当溶液的 pH 达到某一值时，这两者浓度相等，该氨基酸主要以（Ⅱ）形式存在，在电场中，既不移向阳极，也不移向阴极，这时溶液的 pH 叫做该氨基酸的等电点，用符号 IP 表示。通常，中性氨基酸的 IP 在 5.6～6.3，碱性氨基酸约在 7.6～10.8，酸性氨基酸约在 2.8～3.2。处在等电点时，氨基酸的溶解度最小，利用这一性质可分离不同的氨基酸。

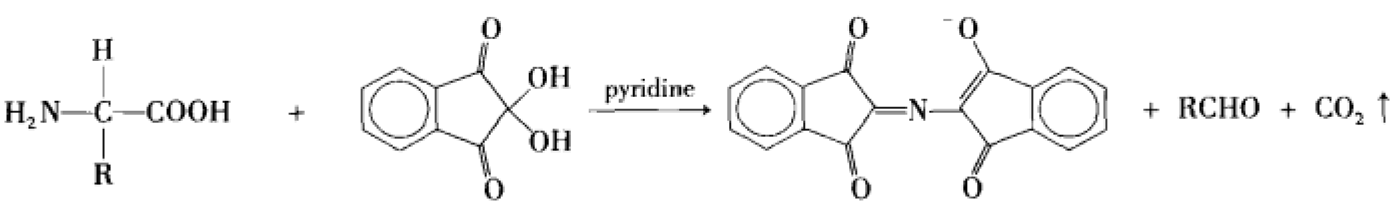
2. 羧基的酯化（esterification of the carboxyl group）：



3. 氨基的酰基化（acylation of the amino group）：



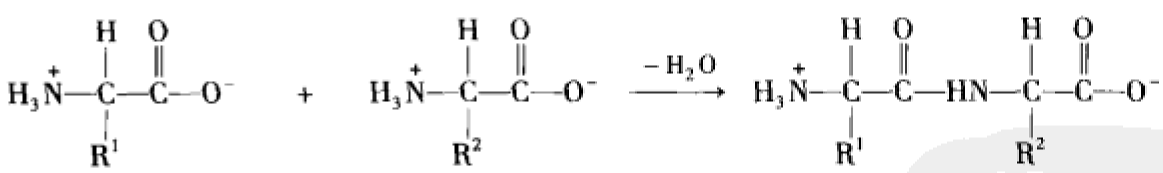
4. 与水合茚三酮的反应（reaction with ninhydrin）：



紫色

☆ 用于 α－氨基酸的鉴别。

5. 肽键的形成（formation of peptide bonds）：



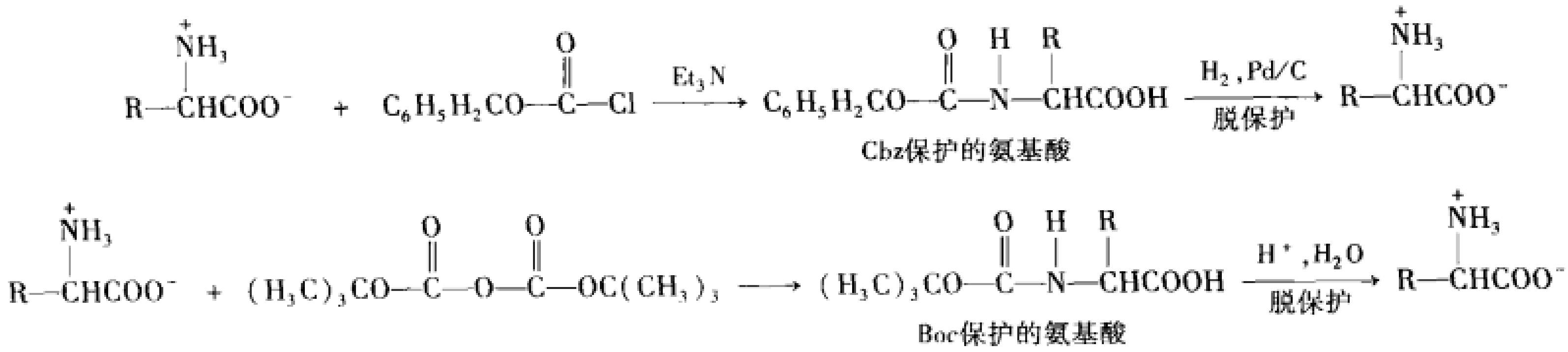
☆ 除以上性质外，氨基酸还具有许多胺和酸的性质。

五、肽（peptide）

1. 肽的结构、分类及命名：α－氨基酸是肽的单体，通过一个氨基酸的羧基与另一个氨基酸的氨基的重复反应构成酰胺链而形成聚合物。连接氨基酸的酰胺键称为肽键，按这种方式连接氨基酸形成的寡聚体称为肽，多聚体称为多肽。例如，两个氨基酸生成二肽，三个氨基酸生成三肽等。形成肽的各个氨基酸单元称为残基。肽的命名是将各个残基的名字简单地按序列连在一起，看做是下一个的取代基，到 C 端残基结束。多肽中氨基酸序列可用简短的三字码或一字码缩写法表述，N 端在左，C 端在右。例如，苯丙氨酰基亮氨酰基苏氨酸可用三字码表示为 Phe-Leu-Thr。多肽的结构是多种多样的，可以是线形的、环状的、二硫键和氢键连接的、β 折叠、α 螺旋等。氨基酸的序列是多肽的一级结构，通过折叠产生二级结构，进一步折叠和卷曲产生三级结构，几个多肽的聚集形成四级结构。

2. 多肽的合成：多肽合成需要末端保护的氨基酸，用 DCC 偶合。产物可在任意一端选择性脱保护，以便链的延长。固体载体的使用，如 Merrifield 合成，可以实现自动化。

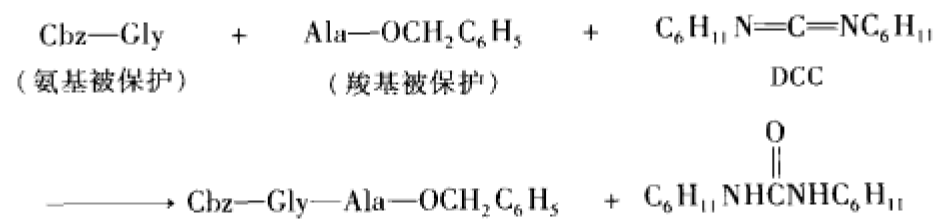
（1）保护氨基的两种常用试剂：氯甲酸苄酯和二叔丁焦碳酸酯。



☆ Boc 保护基的特点是对催化氢化及烯碱都不起作用，只能用温和酸性水解法脱保护。

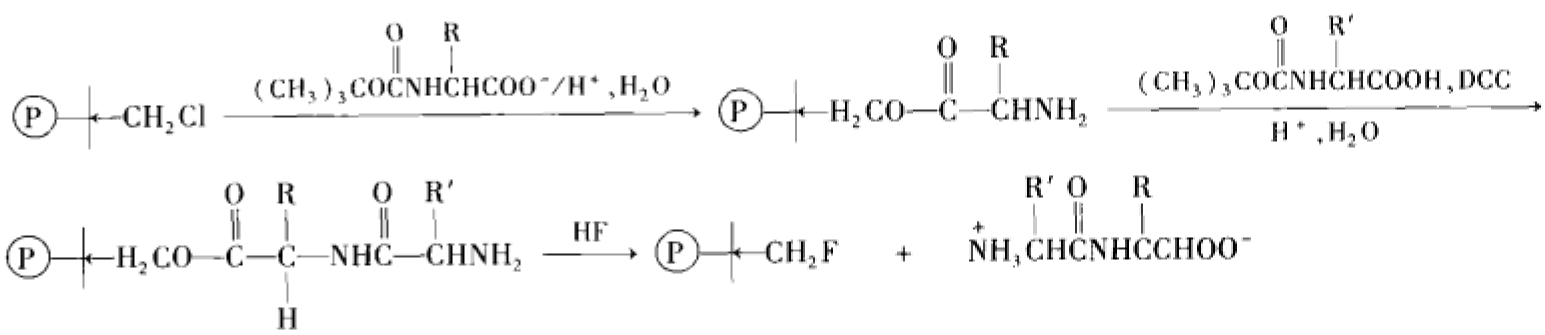
（2）羧基通过将其变成甲酯、乙酯、叔丁酯或苄酯进行保护，然后在温和条件下水解或氢解的方法脱去保护基。

（3）用二环已基碳二亚胺（DCC）形成肽键。例如，



☆ 选择性脱保护，继续与保护的氨基酸反应达到链的延长。

（4）Merrifield 固相合成：



Ⓟ 表示聚苯乙烯

3. 多肽的结构测定：多肽的结构是通过不同的降解方法确定的。首先确定纯的多肽。然后，对有二硫键的多肽，先断裂二硫键，再通过完全水解和氨基酸分析测定组成氨基酸的种类和相对含量。N 端残基可用 Edman 降解来鉴定。重复 Edman 降解给出短肽的序列，这些短肽是通过专一的酶促进水解，从更长的多肽获得的。

Essential Problem-Solving Skills in Chapter 25

1. Correctly name amino acids and peptides, and draw the structures from their names.
2. Use perspective drawings and Fischer projections to show the stereochemistry of D- and L-amino acids.
3. Explain which amino acids are acidic, which are basic, and which are neutral. Use the isoelectric point to predict whether a given amino acid will be positively charged, negatively charged, or neutral at a given pH.
4. Show how one of the following syntheses might be used to make a given amino acid: reductive amination

HVZ followed by ammonia

Gabriel-malonic ester synthesis

Strecker synthesis

5. Predict products of the following reactions of amino acids: esterification, acylation, reaction with ninhydrin.
6. Use information from terminal residue analysis and partial hydrolysis to determine the structure of an unknown peptide.
7. Show how solution-phase peptide synthesis or solid-phase peptide synthesis would be used to make a given peptide. Use appropriate protecting groups to prevent unwanted couplings.
8. Discuss and identify the four levels of protein structure (primary, secondary, tertiary, quaternary). Explain how the structure of a protein affects its properties and how denaturation changes the structure.

Study Problems

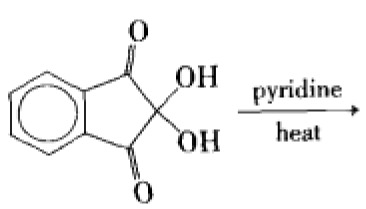
25–19 Define each term and give an example.

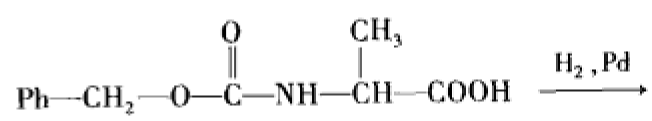
(a) α-amino acid (b) L-amino acid (c) essential amino acid (d) dipolar ion
(e) isoelectric point (f) Strecker synthesis (g) electrophoresis (h) transamination
(i) peptide bond (j) hydrogenolysis (k) enzymatic resolution (l) zwitterion
(m) peptide (n) protein (o) primary structure (p) secondary structure
(q) tertiary structure (r) quaternary structure (s) pleated sheet (t) α helix
(u) conjugated protein (v) protein denaturation (w) disulfide bridge (x) Edman degradation
(y) prosthetic group (z) solid-phase peptide synthesis (aa) oligopeptide (bb) prion protein

25–20 Draw the complete structure of the following peptide.

Ser-Gln-Met·NH_2

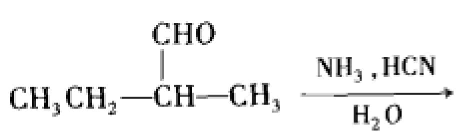
25–21 Predict the products of the following reactions.

(a) Ile + 

(b) 

(c) Lys + excess $(CH_3CO)_2O \longrightarrow$

(d) (D,L)-proline $\xrightarrow[\text{(2) hog kidney acylase, } H_2O]{\text{(1) excess } Ac_2O}$

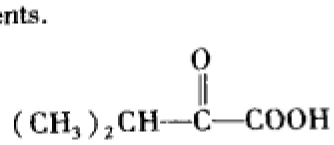
(e) 

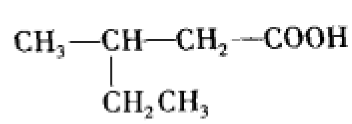
(f) product from part (e) $\xrightarrow{H_3O^+}$

(g) 4-methylpentanoic acid + $Br_2/PBr_3 \longrightarrow$

(h) product from part (g) + excess $NH_3 \longrightarrow$

25–22 Show how you would synthesize any of the standard amino acids from each starting material. You may use any necessary reagents.

(a) 

(b) 

(c) $(CH_3)_2CH—CH_2—CHO$

(d)

25–23 Show how you would convert alanine to the following derivatives. Show the structure of the product in each case.

(a) alanine isopropyl ester (b) *N*-benzoylalanine
(c) *N*-benzyloxycarbonyl alanine (d) *t*-butyloxycarbonyl alanine

25–24 Suggest a method for the synthesis of the unnatural D enantiomer of alanine from the readily available L enantiomer of lactic acid.

$$CH_3—CHOH—COOH$$

lactic acid

25–25 Show how you would use the Gabriel-malonic ester synthesis to make histidine. What stereochemistry would you expect in your synthetic product?

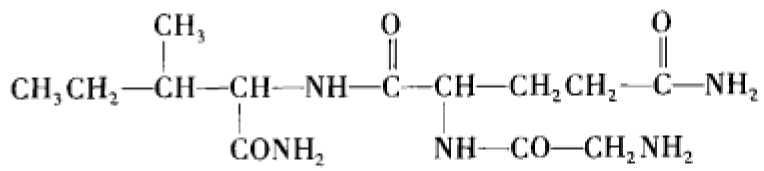
25–26 Show how you would use the Strecker synthesis to make tryptophan. What stereochemistry would you expect in your synthetic product?

25–27 Write the complete structures for the following peptides. Tell whether each peptide is acidic, basic, or neutral.

(**a**) methionylthreonine (**b**) threonylmethionine

(**c**) arginylaspartyllysine (**d**) Glu-Cys-Gln

25–28 The following structure is drawn in an unconventional manner.

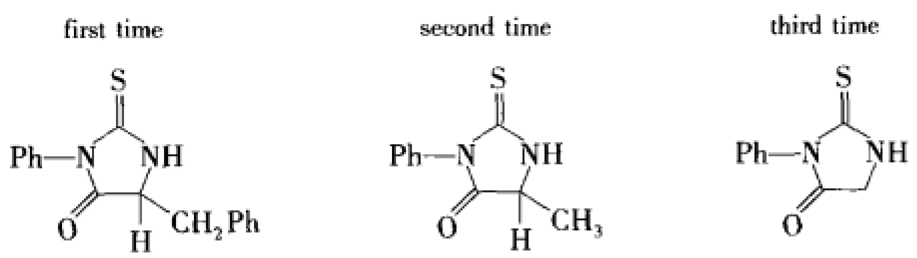


(**a**) Label the N terminus and the C terminus. (**b**) Label the peptide bonds.

(**c**) Identify and label each amino acid present. (**d**) Give the full name and the abbreviated name.

25–29 *Aspartame* (Nutrasweet®) is a remarkably sweet-tasting dipeptide ester. Complete hydrolysis of aspartame gives phenylalanine, aspartic acid, and methanol. Mild incubation with carboxypeptidase has no effect on aspartame. Treatment of aspartame with phenyl isothiocyanate, followed by mild hydrolysis, gives the phenylthiohydantoin of aspartic acid. Propose a structure for aspartame.

25–30 A molecular weight determination has shown that an unknown peptide is a pentapeptide, and an amino acid analysis shows that it contains the following residues: one Gly, two Ala, one Met, one Phe. Treatment of the original pentapeptide with carboxypeptidase gives alanine as the first free amino acid released. Sequential treatment of the pentapeptide with phenyl isothiocyanate followed by mild hydrolysis gives the following derivatives:



Propose a structure for the unknown pentapeptide.

25–31 Show the steps and intermediates in the synthesis of Leu-Ala-Phe

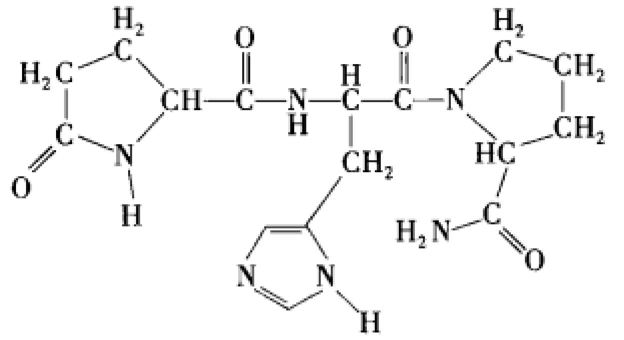
(**a**) by the solution-phase process. (**b**) by the solid-phase process.

25–32 Using classical solution-phase techniques, show how you would synthesize Ala-Val and then combine it with Ile-Leu-Phe to give Ile-Leu-Phe-Ala-Val.

25–33 Peptides often have functional groups other than free amino groups at the N terminus and other than carboxyl groups at the C terminus.

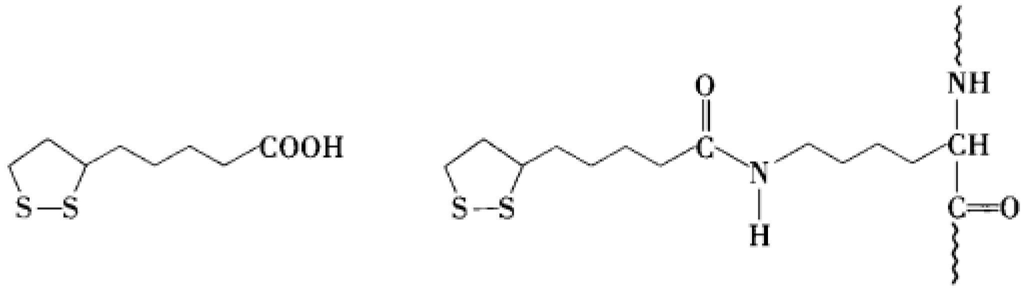
(**a**) A tetrapeptide is hydrolyzed by heating with 6 mol/L HCl, and the hydrolysate is found to contain Ala, Phe, Val, and Glu. When the hydrolysate is neutralized, the odor of ammonia is detected. Explain where this ammonia might have been incorporated in the original peptide.

(**b**) The tripeptide *thyrotropic hormone releasing factor* (TRF) has the full name pyroglutamylhistidylprolinamide. The structure appears here. Explain the functional groups at the N terminus and at the C terminus.



(c) On acidic hydrolysis, an unknown pentapeptide gives glycine, alanine, valine, leucine, and isoleucine. No odor of ammonia is detected when the hydrolysate is neutralized. Reaction with phenyl isothiocyanate followed by mild hydrolysis gives *no* phenylthiohydantoin derivative. Incubation with carboxypeptidase has no effect. Explain these findings.

25−34 Lipoic acid is often found near the active sites of enzymes, usually bound to the peptide by a long, flexible amide linkage with a lysine residue.

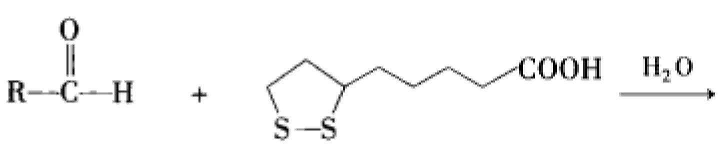


lipoic acid　　　　bound to lysine residue

(a) Is lipoic acid a mild oxidizing agent or a mild reducing agent? Draw it in both its oxidized and reduced forms.

(b) Show how lipoic acid might react with two Cys residues to form a disulfide bridge.

(c) Give a balanced equation for the hypothetical oxidation or reduction, as you predicted in part (a), of an aldehyde by lipoic acid.



25−35 Histidine is an important catalytic residue found at the active sites of many enzymes. In many cases, histidine appears to remove protons or to transfer protons from one location to another.

(a) Show which nitrogen atom of the histidine heterocycle is basic and which is not.

(b) Use resonance forms to show why the protonated form of histidine is a particularly stable cation.

(c) Show the structure that results when histidine accepts a proton on the basic nitrogen of the heterocycle and then is deprotonated on the other heterocyclic nitrogen. Explain how histidine might function as a pipeline to transfer protons between sites within an enzyme and its substrate.

25−36 Metabolism of arginine produces urea and the rare amino acid *ornithine*. Ornithine has an isoelectric point close to 10. Propose a structure for ornithine.

25−37 Glutathione (GSH) is a tripeptide that serves as a mild reducing agent to detoxify peroxides and maintain the cysteine residues of hemoglobin and other red blood cell proteins in the reduced state. Complete hydrolysis of glutathione gives Gly, Glu, and Cys. Treatment of glutathione with carboxypeptidase gives glycine as the first free amino acid released. Treatment of glutathione with phenyl isothiocyanate gives the phenylthiohydantoin of glutamic acid.

(a) Propose a structure for glutathione consistent with this information.

(b) Oxidation of glutathione forms glutathione disulfide (GSSG). Propose a structure for glutathione disulfide, and write a balanced equation for the reaction of glutathione with hydrogen peroxide.

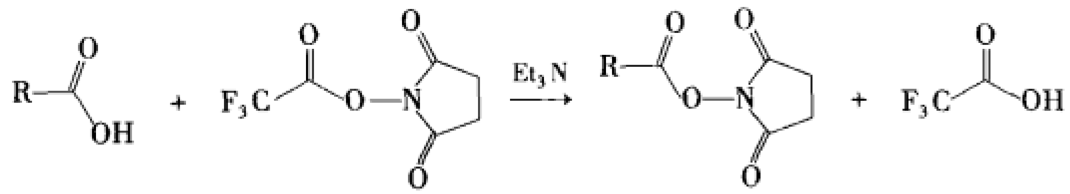
25−38 Complete hydrolysis of an unknown basic decapeptide gives Gly, Ala, Leu, Ile, Phe, Tyr, Glu, Arg, Lys, and Ser. Terminal residue analysis shows that the N terminus is Ala and the C terminus is Ile. Incubation of the decapeptide with chymotrypsin gives two tripeptides, **A** and **B**, and a tetrapeptide, **C**. Amino acid analysis shows that peptide **A** contains Gly, Glu, Tyr, and NH_3; peptide **B** contains Ala, Phe, and Lys; and peptide **C** contains Leu, Ile, Ser, and Arg. Terminal

residue analysis gives the following results.

	N terminus	C terminus
A	Glu	Tyr
B	Ala	Phe
C	Arg	Ile

Incubation of the decapeptide with trypsin gives a dipeptide **D**, a pentapeptide **E**, and a tripeptide **F**. Terminal residue analysis of **F** shows that the N terminus is Ser, and the C terminus is Ile. Propose a structure for the decapeptide and for fragments **A** through **F**.

25−39 There are many methods for activating a carboxylic acid in preparation for coupling with an amine. The following method converts the acid to an *N*-hydroxysuccinimide (NHS) ester.

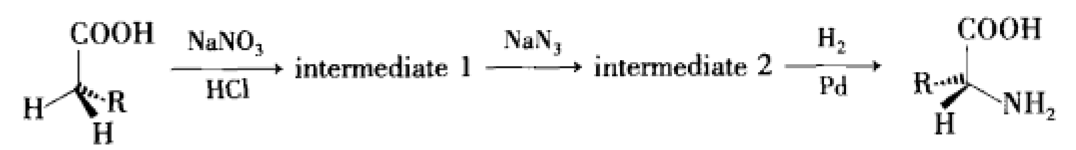


(**a**) Explain why an NHS ester is much more reactive than a simple alkyl ester.

(**b**) Propose a mechanism for the reaction shown.

(**c**) Propose a mechanism for the reaction of the NHS ester with an amine, R—NH_2.

25−40 Sometimes chemists need the unnatural D enantiomer of an amino acid, often as part of a drug or an insecticide. Most L-amino acids are isolated from proteins, but the D amino acids are rarely found in natural proteins. D-amino acids can be synthesized from the corresponding L amino acids. The following synthetic scheme is one of the possible methods.



L configuration D configuration

(**a**) Draw the structures of intermediates 1 and 2 in this scheme.

(**b**) How do we know that the product is entirely the unnatural D configuration?

Chapter 26
Lipids

26－1 Introduction

In our study of organic chemistry, we have usually classified compounds according to their functional groups. Lipids, however, are classified by their solubility: **Lipids** are substances that can be extracted from cells and tissues by nonpolar organic solvents. Steroids, prostaglandins, fats, oil, waxes, terpenes, and even the colorful carotenes in the falling leaves are all lipids.

Lipids include many types of compounds containing a wide variety of functional groups. You could easily prepare a solution of lipids by grinding a T-bone steak in a blender and then extracting the puree with chloroform or diethyl ether. The resulting solution of lipids would contain a multitude of compounds, many with complex structures. To facilitate the study of lipids, chemists have divided this large family into two major classes: complex lipids and simple lipids.

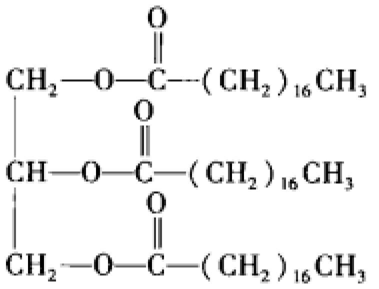
Complex lipids are those that are easily hydrolyzed to simpler constituents. Most complex lipids are esters of long-chain carboxylic acids called *fatty acids*. The two major groups of fatty acid esters are *waxes* and *glycerides*. Waxes are esters of long-chain alcohols, and glycerides are esters of glycerol.

Simple lipids are those that are not easily hydrolyzed by aqueous acid or base. This term often seems inappropriate, because many so-called "simple" lipids are quite complex molecules. We will consider two important groups of simple lipids: steroids and terpenes. Figure 26－1 shows some examples of complex and simple lipids.

26－2 Waxes

Waxes are esters of long-chain fatty acids with long-chain alcohols. They occur widely in nature and serve a number of purposes in plants and animals. *Spermaceti* (Figure 26－1), found in the head of the sperm whale, probably helps to regulate the animal's buoyancy for deep diving. It may also serve to amplify high-frequency sounds for locating prey. *Beeswax* is a mixture of waxes, hydrocarbons, and alcohols that bees use to form their honeycomb. *Carnauba wax* is a mixture of waxes of very high molecular weights. The carnauba plant secretes this waxy material to coat its leaves to prevent excessive loss of water by evaporation. Waxes are also found in the protective coatings of insects' exoskeletons, mammals' fur, and birds' feathers. In contrast to these waxes, the "paraffin wax" used to seal preserves is not a true wax; rather, it is a mixture of high-molecular-weight alkanes.

Examples of complex lipids



tristearin, a fat

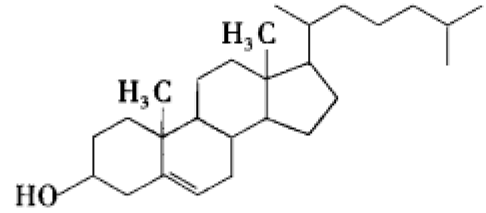
(三硬脂酸甘油酯,脂肪类化合物)

$CH_3(CH_2)_{15}—O—C(=O)—(CH_2)_{14}CH_3$

spermaceti (cetyl palmitate), a wax

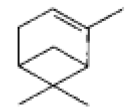
(鲸蜡,鲸蜡醇十六酸酯,蜡类化合物)

Examples of simple lipids



cholesterol, a steroid

[胆甾醇;胆固醇(俗),甾族化合物]



α-pinene, a terpene

(α-蒎烯,萜类化合物)

Figure 26-1 Examples of lipids (类脂).

$CH_3(CH_2)_{29}—O—C(=O)—(CH_2)_{24}CH_3$

a component of beeswax (蜂蜡)

$CH_3(CH_2)_{33}—O—C(=O)—(CH_2)_{26}CH_3$

a component of carnauba wax (加洛巴蜡;巴西棕榈蜡)

For many years, natural waxes were used in making cosmetics, adhesives, varnishes, and waterproofing materials. Synthetic materials have now replaced natural waxes for most of these uses.

26-3 Triglycerides

Glycerides are simply fatty acid esters of the triol *glycerol*. The most common glycerides are **triglycerides (triacylglycerols)**, in which all three of the glycerol —OH groups have been esterified by fatty acids. For example, tristearin (Figure 26-1) is a component of beef fat in which all three —OH groups of glycerol are esterified by stearic acid, $CH_3(CH_2)_{16}COOH$.

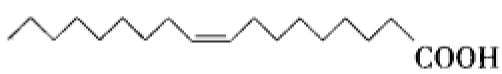
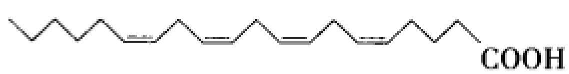
Triglycerides are commonly called **fats** if they are solid at room temperature and **oils** if they are liquid at room temperature. Most triglycerides derived from mammals are fats, such as beef fat or lard. Although these fats are solid at room temperature, the warm body temperature of the living animal keeps them somewhat fluid, allowing for body movement. In plants and cold-blooded animals, triglycerides are generally oils, such as corn oil, peanut oil, or fish oil. A fish requires liquid oils rather than solid fats because it would have difficulty moving if its triglycerides solidified whenever it swam in a cold stream.

Fats and oils are commonly used for long-term energy storage in plants and animals. Fat is a more efficient source of long-term energy than carbohydrates because metabolism of a gram of fat releases over twice as much energy as a gram of sugar or starch. An average 70-kg adult male stores about 4000 kJ of readily available energy as glycogen (0.2 kg), and about 600000 kJ of long-term energy as fat (15 kg): enough to supply his resting metabolic needs for nearly three months!

The **fatty acids** of common triglycerides are long, unbranched carboxylic acids with about 12 to 20 carbon atoms. Most fatty acids contain even numbers of carbon atoms because they are derived from two-carbon acetic acid units. Some of the common fatty acids have saturated carbon chains, while others have one or more carbon-carbon double bonds. Table 26-1 shows the structures of some common fatty acids derived from fats and oils.

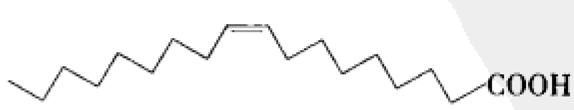
Table 26-1 shows that saturated fatty acids have melting points that increase gradually with their molecular weights. The presence of a cis double bond lowers the melting point, however. Notice that the 18-carbon saturated acid (stearic acid) has a melting point of 70 ℃, while the 18-carbon acid with a cis double bond (oleic acid) has a melting point of 4 ℃. This lowering of the melting point results from the unsaturated acid's "kink" at the position of the double bond. Kinked molecules cannot pack as tightly together in a solid as the uniform zigzag chains of a saturated acid.

TABLE 26-1 Structures and Melting Points of Some Common Fatty Acids

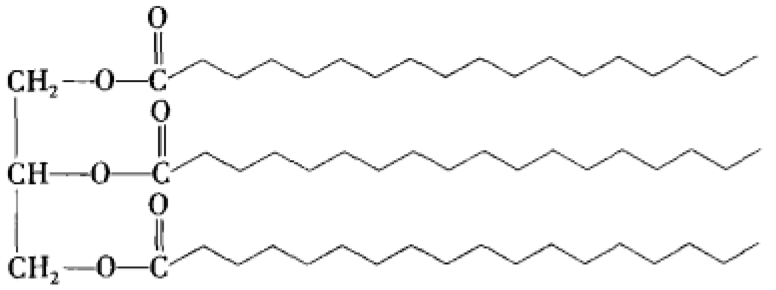
Name	Carbons	Structure	Melting Point/℃
Saturated acids			
lauric acid (月桂酸)	12		44
myristic acid (肉豆蔻酸)	14		59
palmitic acid (软脂酸)	16		64
stearic acid (硬脂酸)	18		70
arachidic acid (花生酸)	20		76
Unsaturated acids			
oleic acid (油酸)	18		4
linoleic acid (亚油酸)	18		-5
linolenic acid (亚麻酸)	18		-11
eleostearic acid (桐油酸)	18		49
arachidonic acid (花生四烯酸)	20		-49

A second double bond lowers the melting point further (linoleic acid, mp -5 ℃), and a third double bond lowers it still further (linolenic acid, mp -11 ℃). The trans double bonds in eleostearic acid (mp 49 ℃) have a smaller effect on the melting point than the cis double bonds of linolenic acid. The geometry of a trans double bond is similar to the zigzag conformation of a saturated acid, so it does not kink the chain as much as a cis double bond.

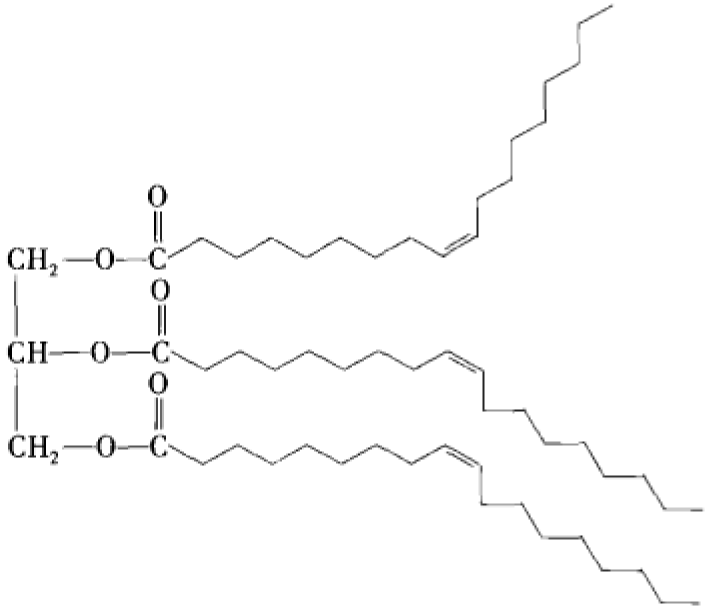
stearic acid, mp 70 ℃
(硬脂酸)



oleic acid, mp 4 ℃
(油酸)



tristearin, mp 72 ℃
(三硬脂酸甘油酯)



triolein, mp −4 ℃
(三油酸甘油酯)

The melting points of fats and oils also depend on the degree of unsaturation (especially cis double bonds) in their fatty acids. A triglyceride derived from saturated fatty acids has a higher melting point because it packs more easily into a solid lattice than a triglyceride derived from kinked, unsaturated fatty acids. Tristearin (mp 72 ℃) is a saturated fat that packs well in a solid lattice. Triolein (mp −4 ℃) has the same number of carbon atoms as tristearin, but triolein has three cis double bonds, whose kinked conformations prevent optimum packing in the solid.

Most saturated triglycerides are *fats* because they are solid at room temperature. Most triglycerides with several unsaturations are *oils* because they are liquid at room temperature. The term *polyunsaturated* simply means there are several double bonds in the fatty acids of the triglyceride.

Most naturally occurring fats and oils are mixtures of triglycerides containing a variety of saturated and unsaturated fatty acids. In general, oils from plants and cold-blooded animals contain more unsaturations than fats from warm-blooded animals. Table 26−2 gives the approximate composition of the fatty acids obtained from hydrolysis of some common fats and oils.

TABLE 26−2 Fatty Acid Composition of Some Fats and Oils, Percent by Weight

Source	Saturated Fatty Acids				Unsaturated Fatty Acids		
	Lauric	Myristic	Palmitic	Stearic	Oleic	Linoleic	Linolenic
beef fat (牛脂;牛油)	0	6	27	14	49	2	0
lard (猪脂)	0	1	24	9	47	10	0
human fat (人脂)	1	3	27	8	48	10	0
herring oil (鲱鱼油)	0	5	14	3	0	0	30[a]

Continue

Source	Saturated Fatty Acids				Unsaturated Fatty Acids		
	Lauric	Myristic	Palmitic	Stearic	Oleic	Linoleic	Linolenic
corn oil（玉米油）	0	1	10	3	50	34	0
olive oil（橄榄油）	0	0.1	7	2	84	5	2
soybean oil（大豆油）	0.2	0.1	10	2	29	51	7
canola oil（低芥酸菜子油）	0	0	2	7	54	30	7
linseed oil（亚麻子油）	0	0.2	7	1	20	20	52

[a]Contains large amounts of even more highly unsaturated fatty acids.

For many years, *lard* (a soft, white solid obtained by rendering pig fat) was commonly used for cooking and baking. Although vegetable oil could be produced more cheaply and in greater quantities, consumers were unwilling to use vegetable oils because they were accustomed to using white, creamy lard. Then vegetable oils were treated with hydrogen gas and a nickel catalyst, reducing some of the double bonds to give a creamy, white *vegetable shortening* that resembles lard. This "partially hydrogenated vegetable oil" largely replaced lard for cooking and baking. *Margarine* is a similar material flavored with butyraldehyde to give it a taste like that of butter.

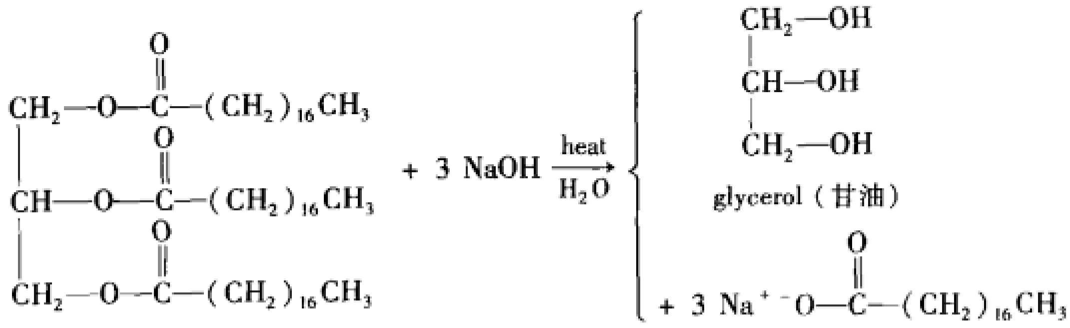
More recently, consumers have learned that "polyunsaturated" vegetable oils are more easily digested, prompting a switch to natural vegetable oils. Some consumers are also concerned with the presence of unnatural trans fatty acids in "partially hydrogenated vegetable oil." During the hydrogenation process, the catalyst lowers the activation energy of both the forward (hydrogenation) and reverse (dehydrogenation) processes. The naturally occurring cis double bonds in vegetable oils can hydrogenate and the products can dehydrogenate. The double bonds end up in random positions, with either cis or trans stereochemistry. The white, creamy product has fewer double bonds overall, but some of the remaining double bonds may be in positions or stereochemical configurations that never occur in nature.

PROBLEM 26-1

Give an equation for the complete hydrogenation of triolein using an excess of hydrogen.
What is the name of the product, and what are the melting points of the starting material and the product?

26-4 Saponification of Fats and Oils; Soaps and Detergents

Saponification is the base-promoted hydrolysis of the ester linkages in fats and oils. One of the products is soap, and the word *saponification* is derived from the Latin word *saponis*, meaning "soap." Saponification was discovered (before 500 B.C.), when it was found that a curdy material resulted when animal fat was heated with wood ashes. Alkaline substances in the ashes promote hydrolysis of the ester linkages of the fat. Soap is currently made by boiling animal fat or vegetable oil with a solution of sodium hydroxide. The following reaction shows formation of soap from tristearin, a component of beef fat.



tristearin, a fat (三硬脂酸甘油酯) — glycerol (甘油) — sodium stearate, a soap (硬脂酸钠)

Chemically, a **soap** is the sodium or potassium salt of a fatty acid. The negatively charged carboxylate group is **hydrophilic** ("attracted to water"), and the long hydrocarbon chain is **hydrophobic** ("repelled by water") and **lipophilic** ("attracted to oils").

In water, soap forms a cloudy solution of **micelles**: clusters of about 100 to 200 soap molecules with their polar "heads" (the carboxylate groups) on the surface of the cluster and their hydrophobic "tails" (the hydrocarbon chains) enclosed within. The micelle is an energetically stable particle because the hydrophilic groups are hydrogen-bonded to the surrounding water, while the hydrophobic groups are shielded within the interior of the micelle, interacting with other hydrophobic groups.

Soaps are useful cleaning agents because of the different affinities of a soap molecule's two ends. Greasy dirt is not easily removed by pure water because grease is hydrophobic and insoluble in water. The long hydrocarbon chain of a soap molecule dissolves in the grease, with the hydrophilic head at the surface of the grease droplet. Once the surface of the grease droplet is covered by many soap molecules, a micelle can form around it with a tiny grease droplet at its center. This grease droplet is easily suspended in water because it is covered by the hydrophilic carboxylate groups of the soap. The resulting mixture of two insoluble phases (grease and water), with one phase dispersed throughout the other in small droplets, is called an **emulsion**. We say the grease has been **emulsified** by the soapy solution. When the wash water is rinsed away, the grease goes with it.

The usefulness of soaps is limited by their tendency to precipitate out of solution in hard water. **Hard water** is water that is acidic or that contains ions of calcium, magnesium, or iron. In acidic water (such as the "acid rain" of environmental concern), soap molecules are protonated to the free fatty acids. Without the ionized carboxylate group, the fatty acid floats to the top as a greasy "acid scum" precipitate.

$$\underset{\text{a soap}}{CH_3(CH_2)_n\text{—}\overset{O}{\overset{\|}{C}}\text{—}O^- \ {}^+Na} + H^+ \longrightarrow \underset{\text{acid scum}}{CH_3(CH_2)_n\text{—}\overset{O}{\overset{\|}{C}}\text{—}OH\downarrow} + Na^+$$

Many areas have household water containing calcium, magnesium, and iron ions. Although these mineral-rich waters can be healthful for drinking, the ions react with soaps to form insoluble salts called *hard-water scum*. The following equation shows the reaction of a soap with calcium, common in areas where water comes in contact with limestone rocks.

$$2\ \underset{\text{a soap}}{CH_3(CH_2)_n\text{—}\overset{O}{\overset{\|}{C}}\text{—}O^- \ {}^+Na} + Ca^{2+} \longrightarrow \underset{\text{hard-water scum}}{\left[CH_3(CH_2)_n\text{—}\overset{O}{\overset{\|}{C}}\text{—}O \right]_2 Ca\downarrow} + 2\ Na^+$$

PROBLEM 26-2

Give equations to show the reactions of sodium stearate with

(**a**) Ca^{2+} (**b**) Mg^{2+} (**c**) Fe^{3+}

PROBLEM 26-3

Several commercial laundry soaps contain water-softening agents, usually sodium carbonate (Na_2CO_3) or sodium phosphate (Na_3PO_4 or Na_2HPO_4). Explain how these water-softening agents allow soaps to be used in water that is hard by virtue of its

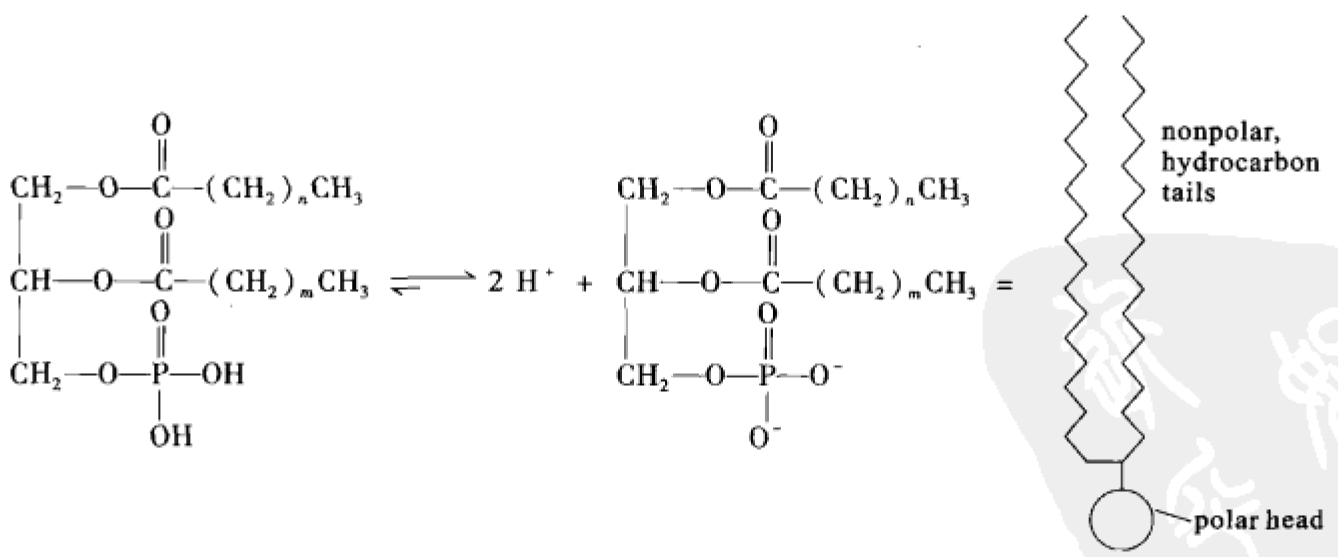
(**a**) low pH (**b**) dissolved Ca^{2+}, Mg^{2+}, and Fe^{3+} salts

Soaps precipitate in hard water because of the chemical properties of the carboxylic acid group. **Synthetic detergents** avoid precipitation by using other functional groups in place of carboxylic acid salts. Sodium salts of sulfonic acids are the most widely used class of synthetic detergents. Sulfonic acids are more acidic than carboxylic acids, so their salts are not protonated, even in strongly acidic wash water. Calcium, magnesium, and iron salts of sulfonic acids are soluble in water, so sulfonate salts can be used in hard water without forming a scum.

Like soaps, synthetic detergents combine hydrophilic and hydrophobic regions in the same molecule. Hydrophobic regions are generally alkyl groups or aromatic rings. Hydrophilic regions may contain anionic groups, cationic groups, or nonionic groups containing several oxygen atoms of other hydrogen-bonding atoms.

26-5 Phospholipids

Phospholipids are lipids that contain groups derived from phosphoric acid. The most common phospholipids are **phosphoglycerides**, which are closely related to common fats and oils. A phosphoglyceride generally has a phosphoric acid group in place of one of the fatty acids of a triglyceride. The simplest class of phosphoglycerides are **phosphatidic acids**, which consist of glycerol esterified by two fatty acids and one phosphoric acid group. Although it is often drawn in its acid form, a phosphatidic acid is actually deprotonated at neutral pH.

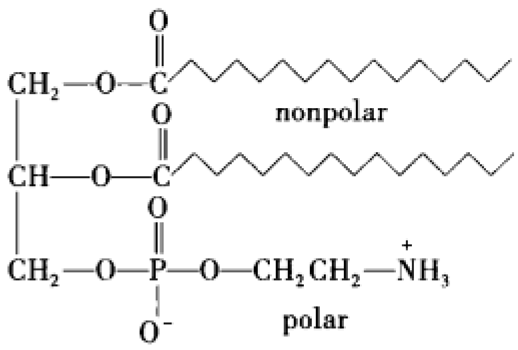


a phosphatidic acid (磷脂酸) ionized form schematic representation

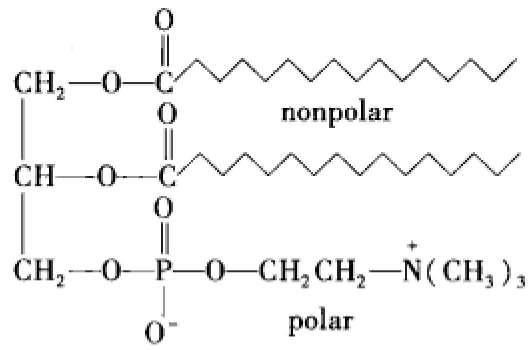
Many phospholipids contain an additional alcohol esterified to the phosphoric acid group. **Cephalins** are esters of ethanolamine, and **lecithins** are esters of choline. Both cephalins and lecithins are widely found in plant and animal tissues.

$HO{-}CH_2CH_2{-}NH_2$ $HO{-}CH_2CH_2{-}\overset{+}{N}(CH_3)_3$

ethanolamine (乙醇胺) choline (胆碱)



a cephalin (脑磷脂),
or phosphatidyl ethanolamine
(磷脂酰乙醇胺)



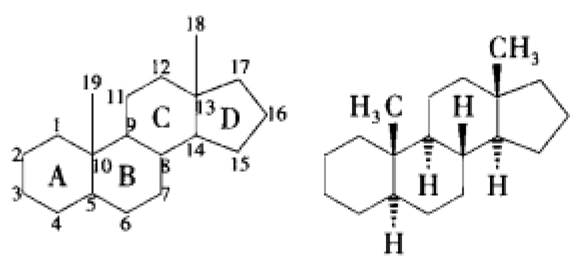
a lecithin (卵磷脂),
or phosphatidyl choline
(磷脂酰胆碱)

Like phosphatidic acids, lecithins and cephalins contain a polar "head" and two long, nonpolar hydrocarbon "tails." This soap-like structure gives phospholipids some interesting properties. Like soaps, they form micelles and other aggregations with their polar heads on the outside and their nonpolar tails protected on the inside.

Another stable form of aggregation is a lipid bilayer, with the heads on the two surfaces of a membrane, and the hydrophobic tails are protected within. Cell membranes contain phosphoglycerides oriented in a lipid bilayer, forming a barrier that restricts the flow of water and dissolved substances.

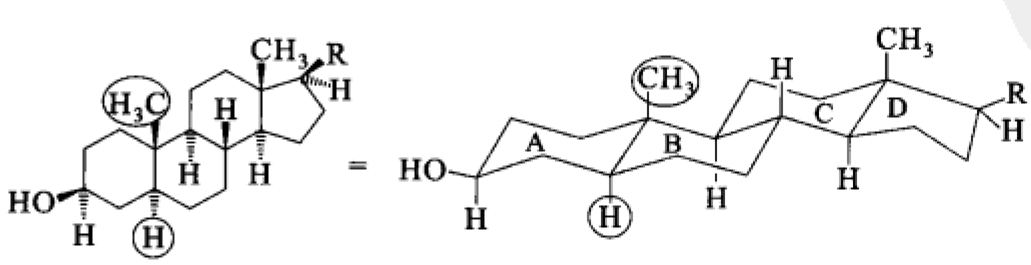
26-6 Steroids

Steroids are complicated polycyclic molecules found in all plants and animals. They are classified as *simple lipids* because they do not undergo hydrolysis like fats, oils, and waxes do. Steroids encompass a wide variety of compounds, including hormones, emulsifiers, and components of membranes. Steroids are compounds whose structures are based on the tetracyclic androstane ring system, shown here. The four rings are designated A, B, C, and D, beginning with the ring at lower left, and the carbon atoms are numbered beginning with the A ring and ending with the two "angular" (axial) methyl groups.



androstane [雄(甾)烷]

Each of the three ring junctions is trans in the androstane structure shown above. Most steroids have this all-trans structure, which results in a stiff, nearly flat molecule with the two axial methyl groups perpendicular to the plane. In some steroids, the junction between rings A and B is cis, requiring the A ring to fold down below the rest of the ring system. Figure 26-2 shows the androstane ring system with both trans and cis A-B ring junctions. The B-C and C-D ring junctions are nearly always trans in natural steroids.



a trans A-B steroid (A-B 反式甾族化合物)

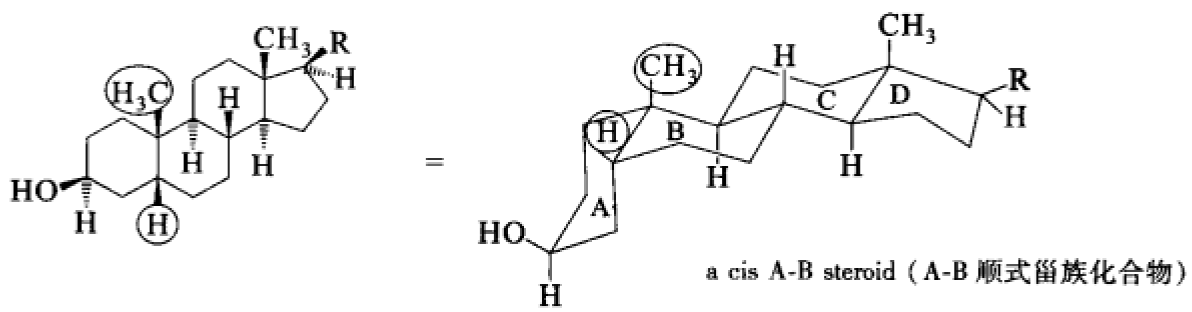
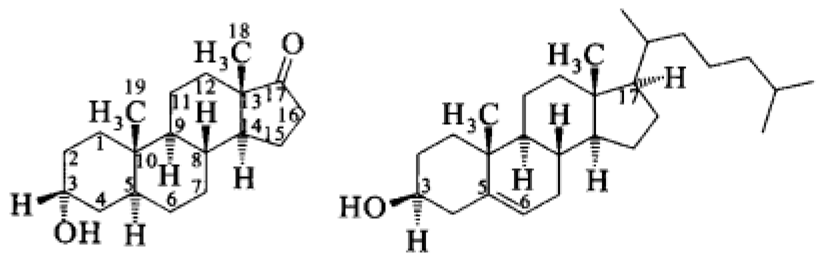


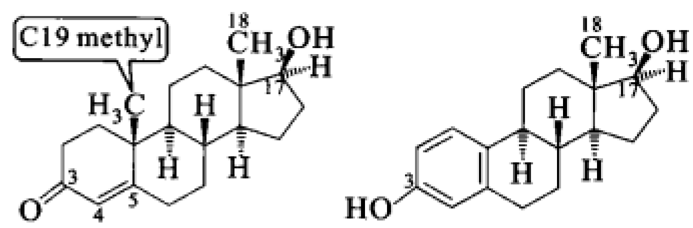
Figure 26−2 Common steroids may have either a cis or a trans A-B ring junction.

Most steroids have an oxygen functional group (═O or —OH) at C3 and some kind of side chain or other functional group at C17. Many also have a double bond from C5 to either C4 or C6. The structures of androsterone and cholesterol serve as examples. Androsterone, a male sex hormone, is based on the simple androstane ring system. Cholesterol is a common biological intermediate and is believed to be the biosynthetic precursor to other steroids. It has a side chain at C17 and a double bond between C5 and C6.



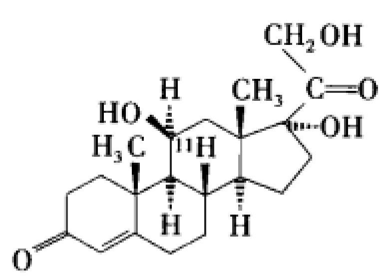
androsterone [雄(甾)酮]　　　cholesterol (胆甾醇)

The principal sex hormones have been characterized and studied extensively. Testosterone is the most potent of the natural male sex hormones, and estradiol is the most potent natural female hormone. Notice that the female sex hormone differs from the male hormone by its aromatic A ring. For the A ring to be aromatic, the C19 methyl group must be lost. In mammals, testosterone is converted to estradiol in the female's ovaries, where enzymes remove C19 and two hydrogen atoms to give the aromatic A ring.



testosterone (睾丸酮)　　　estradiol (雌二醇)

Some of the most important physiological steroids are the adrenocortical hormones, synthesized by the adrenal cortex. Most of these hormones have either a carbonyl group or a hydroxyl group at C11 of the steroid skeleton. The principal adrenocortical hormone is cortisol, used for the treatment of inflammatory diseases of the skin (psoriasis), the joints (rheumatoid arthritis), and the lungs (asthma).

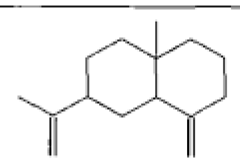
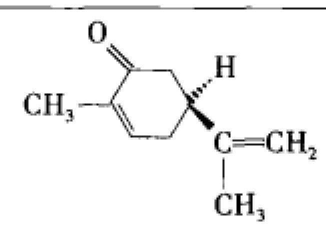
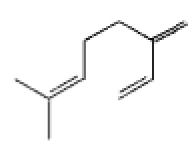
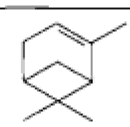


cortisol (可的松)

26−7 Terpenes

Terpenes are a diverse family of compounds with carbon skeletons composed of five-carbon isopentyl (isoprene) units. Terpenes are commonly isolated from the **essential oils** of plants: the fragrant oils that are isolated from plant material by steam distillation. The term *essential oils* literally means "oils derived from the essence" of plants. They often have pleasant tastes or aromas, and they are widely used as flavorings, deodorants, and medicines. Table 26−3 lists several common types of essential oils and their principal components.

TABLE 26−3 Some Useful Essential Oils

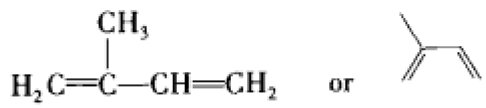
Essential Oil	Source	Major Components
perfume	flowers	mixtures of terpenes and terpenoids
oil of turpentine	evergreens	mixtures of terpenes and terpenoids
oil of celery (芹菜油)	celery (芹菜)	 β-selinene, a terpene [β−蛇床烯(芹子烯),萜类化合物]
caraway oil (蒿子油)	caraway seed (蒿籽)	 (+)-carvone, a terpene (香芹酮)
oil of bay (月桂油)	bay leaves 月桂叶子	 myrcene, a terpene (月桂烯)
cedar leaf oil (雪松叶油)	leaves of the "white cedar" (actually a pine)	 α-pinene, a terpene (α−蒎烯)

26−7A Characteristics and Nomenclature of Terpenes

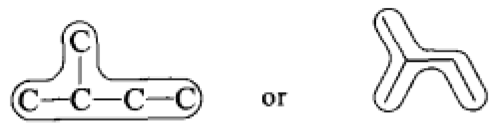
Hundreds of essential oils were used as perfumes, flavorings, and medicines for centuries before chemistry was capable of studying the mixtures. In 1818, it was found that oil of turpentine has a C:H ratio of 5:8, and many other essential oils have similar C:H ratios. This group of piney-smelling natural products with similar C:H ratios came to be known as **terpenes.**

In 1887, German chemist Otto Wallach determined the structures of several terpenes and discovered that all of them are formally composed of two or more five-carbon units of **isoprene** (2-methyl-1, 3-butadiene). The isoprene unit maintains its isopentyl structure in a terpene, usually with modification of the isoprene double bonds.

Isoprene

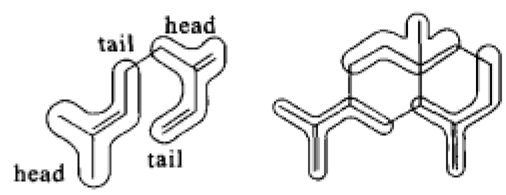


An isoprene unit



head tail (may have double bonds)

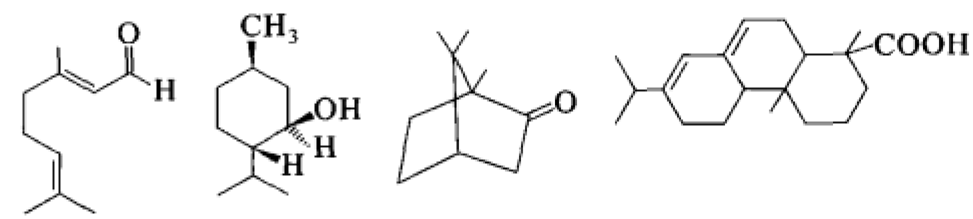
The isoprene molecule and the isoprene unit are said to have a "head" (the branched end) and a "tail" (the unbranched ethyl group). Myrcene can be divided into two isoprene units, with the head of one unit bonded to the tail of the other.



myrcene (月桂烯) β-selinene (β-蛇床烯)

β-Selinene has a more complicated structure, with two rings and a total of 15 carbon atoms. Nevertheless, β-selinene is composed of three isoprene units. Once again, these three units are bonded head to tail, although the additional bonds used to form the rings make the head-to-tail arrangement more difficult to see.

Many terpenes contain additional functional groups, especially carboxyl groups and hydroxyl groups. A terpene aldehyde, a terpene alcohol, a terpene ketone, and a terpene acid are shown next.



geranial (香叶醛;牻牛儿醛) menthol (薄荷醇) camphor (樟脑) abietic acid [枞酸(松香酸)]

PROBLEM 26-4

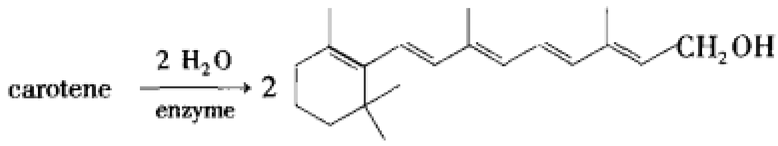
Circle the isoprene units in geranial, menthol, camphor, and abietic acid.

26-7B Classification of Terpenes

Terpenes are classified according to the number of carbon atoms, in units of ten. A terpene with 10 carbon atoms (two isoprene units) is called a **monoterpene**, one with 20 carbon atoms (four isoprene units) is a **diterpene**, and so on. Terpenes with 15 carbon atoms (three isoprene units) are called **sesquiterpenes**, meaning that they have $1\frac{1}{2}$ times 10 carbon

Class Name	Carbons
monoterpenes (单萜)	10
sesquiterpenes (倍半萜)	15
diterpenes 双萜(二萜)	20
triterpenes 三萜	30
tetraterpenes 四萜	40

atoms. Myrcene, geranial, menthol, and camphor are monoterpenes, β-selinene is a sesquiterpene, abietic acid is a diterpene, and squalene (Figure 26−3) is a **triterpene**.



(胡萝卜素) retinol (vitamin A) [视黄醇(维生素A)]

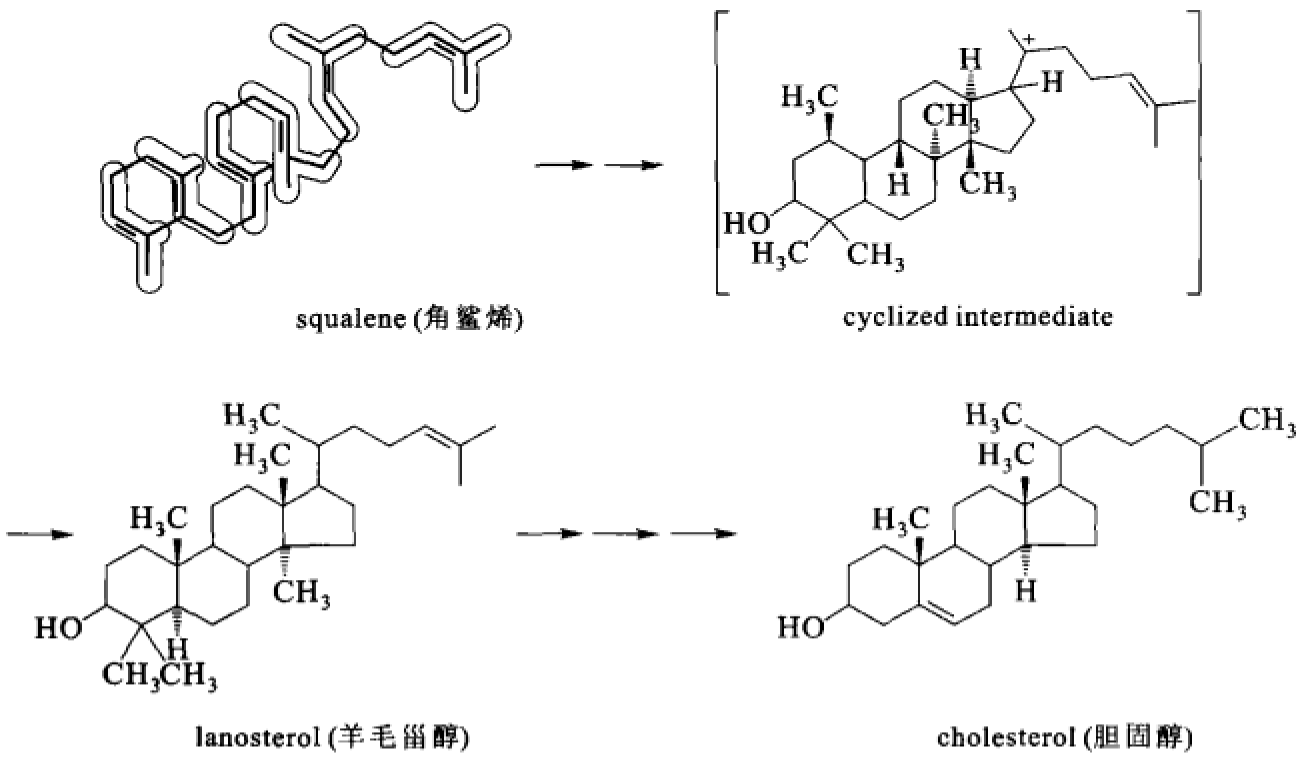
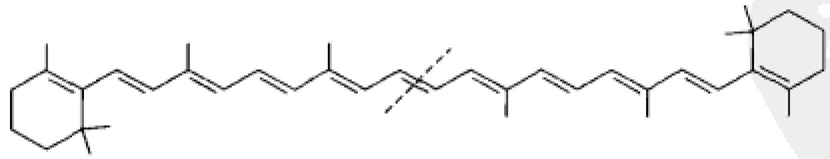


Figure 26−3 Cholesterol is a triterpenoid that has lost three carbon atoms from the original six isoprene units of squalene. Another carbon atom has migrated to form the axial methyl group between rings C and D.

Carotenes, with 40 carbon atoms, are tetraterpenes. Their extended system of conjugated double bonds moves the intense $\pi \rightarrow \pi^*$ ultraviolet absorption into the visible region, making them brightly colored. Carotenes are responsible for the pigmentation of carrots, tomatoes, and squash, and they help to give tree leaves their fiery colors in autumn. β-Carotene is the most common carotene isomer. It can be divided into two head-to-tail diterpenes, linked tail to tail.



β-carotene: λ_{max} = 454 nm, κ = 140000 L/(mol·cm)
(β-胡萝卜素)

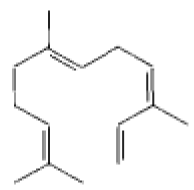
PROBLEM 26−5

Circle the eight isoprene units in β-carotene.

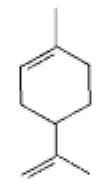
Carotenes are believed to be biological precursors of retinol, commonly known as vitamin A. If a molecule of β-carotene is split in half at the tail-to-tail linkage, each of the diterpene fragments may be converted to retinol.

PROBLEM 26-6

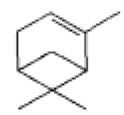
1. Circle the isoprene units in the following terpenes.
2. Classify each of these as a monoterpene, diterpene, etc.



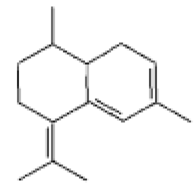
(a) α-farnesene (法呢烯)
(from oil of citronella)



(b) limonene (苧烯)
(from oil of lemon)



(c) α-pinene (蒎烯)
(from turpentine)



(d) zingiberene (姜烯)
(from oil of ginger)

26-7C Terpenoids

Many natural products are derived from terpenes, even though they do not have carbon skeletons composed exclusively of C_5 isoprene units. These terpene-like compounds are called **terpenoids**. They may have been altered through rearrangements, loss of carbon atoms, or introduction of additional carbon atoms. Cholesterol is an example of a terpenoid that has lost some of the isoprenoid carbon atoms.

Figure 26-3 shows that cholesterol is a triterpenoid, formed from six isoprene units with loss of three carbon atoms. The six isoprene units are bonded head to tail, with the exception of one tail-to-tail linkage. The triterpene precursor of cholesterol is believed to be squalene. We can envision an acid-catalyzed cyclization of squalene to give an intermediate that is later converted to cholesterol with loss of three carbon atoms.

Summary in Chinese

本章概要

类脂是指用非极性有机溶剂萃取生物原料所得到的多种化合物的统称。例如:蜡、甘油酯(包括磷脂)、萜类及甾族化合物等可溶于非极性溶剂中的生物分子。

一、蜡(wax)

由长链脂肪酸和长链醇所形成的酯称为蜡。蜡有很多用途,如巴西棕榈蜡具有保持高光泽的能力,硬且抗水,用于地板蜡和汽车蜡。鲸蜡和蜂蜡是液体或很软的固体,可用作润滑剂。

二、甘油三酯(triglyceride)

1,2,3-丙三醇(甘油)和长链脂肪酸形成的三酯称为甘油三酯。甘油三酯有甘油同酸酯和甘油混酸酯之分,天然的甘油三酯主要是甘油混酸酯。在室温下为固体的甘油三酯称为脂肪;在室温下为液体的甘油三酯称为油。甘油三酯中的脂肪酸通常是12~20个偶数碳原子的正构羧酸,如果含有双键,通常为顺式。甘油三酯可以发生水解、皂化、酯交换反应。

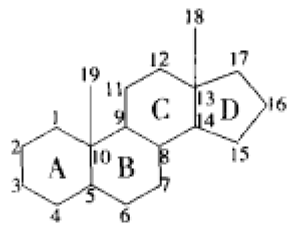
三、磷脂(phospholipid)

磷脂是含有磷酸衍生物的类脂,最常见的是磷酸甘油酯。在磷酸甘油酯中,甘油的两个相邻羟基被两个脂肪酸酯化,另一个羟基被磷酸衍生物酯化,其中磷酸衍生物中带有一个由相对分子质量较低的醇衍生的取代基如乙醇胺、胆碱等。磷脂在水溶液中能形成类脂双层,与酸或碱作用均可成盐,有乳化性,可发生皂化、水解反应。

四、甾族化合物(steroid)

甾族化合物是指具有下面基本结构的化合物,可看做是环戊烷并高氢化菲的一大类化合物。表示甾

族化合物的构型时，常以 A、B 环之间的甲基(19 号)为标准，把它排在环系平面的上面，用实线表示；其他基团凡是与这个甲基在环平面的同一边时，都用实线表示；否则，用虚线表示。通常，B 环和 C 环，及 C 环和 D 环都以反位相稠合，A 环和 B 环可以是顺位或反位相稠合。



五、萜(terpene)

以异戊二烯的碳架为基本单位首尾相连形成的化合物及其含氧衍生物统称为萜。根据分子中异戊二烯单位的数目可分为单萜、倍半萜、二萜、三萜等。萜类化合物广泛分布于植物、昆虫、微生物等动植物体内。

Essential Problem-Solving Skills in Chapter 26

1. Classify lipids both into the large classifications (such as simple lipids, complex lipids, phospholipids, etc.) and into the more specific classifications (such as waxes, triglycerides, cephalins, lecithins, steroids, prostaglandins, terpenes, etc.).
2. Predict the physical properties of fats and oils from their structures.
3. Identify the isoprene units in terpenes, and classify terpenes according to the number of carbon atoms.
4. Predict the products of reactions of lipids with standard organic reagents. In particular, consider the reactions of the ester and olefinic groups of glycerides and the carboxyl groups of fatty acids.
5. Explain how soaps and detergents work, with particular attention to their similarities and differences.

Study Problems

26−7 Define each term and give an example.

(a) lipid	**(b)** fat	**(c)** oil	**(d)** fatty acid
(e) wax	**(f)** soap	**(g)** detergent	**(h)** hard water
(i) micelle	**(j)** emulsion	**(k)** lipid bilayer	**(l)** lecithin
(m) cephalin	**(n)** phospholipid	**(o)** triglyceride	**(p)** simple lipid
(q) complex lipid	**(r)** prostaglandin	**(s)** steroid	**(t)** terpene

26−8 Give the general classification of each compound.

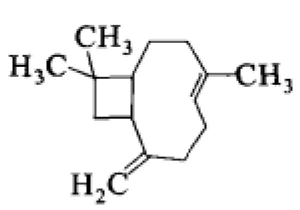
(a) glyceryl tripalmitate

(b) $CH_3—(CH_2)_{10}—CH_2—O—\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}—O^{-}\ ^{+}Na$

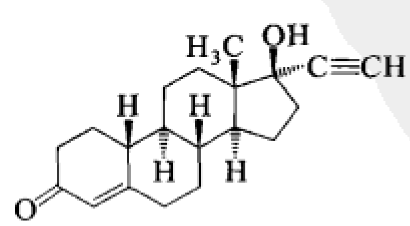
sodium lauryl sulfate (in shampoo)

(c) $CH_3—(CH_2)_{13}—O—\overset{O}{\overset{\|}{C}}—(CH_2)_{16}—CH_3$

tetradecyl octadecanoate

(d) 

caryophyllene (from cloves)

(e) 

norethindrone

(a synthetic hormone)

26−9 Predict the products obtained from the reaction of triolein with the following reagents.

(a) NaOH in water (b) H_2 and a nickel catalyst (c) Br_2 in CCl_4
(d) ozone, then dimethyl sulfide (e) warm $KMnO_4$ in water (f) $CH_2I_2/Zn(Cu)$
(g) saponification, then $LiAlH_4$

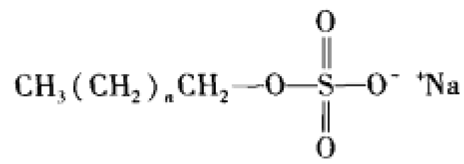
26−10 Show how you would convert oleic acid to the following fatty acid derivatives.

(a) 1-octadecanol (b) stearic acid (c) octadecyl stearate
(d) nonanal (e) nonanedioic acid (f) 2,9,10-tribromostearic acid

26−11 Phospholipids undergo saponification much like triglycerides. Draw the structure of a phospholipid meeting the following criteria. Then draw the products that would result from its saponification.

(a) a cephalin containing stearic acid and oleic acid (b) a lecithin containing palmitic acid

26−12 Some of the earliest synthetic detergents were the sodium alkyl sulfates.



Show how you would make sodium octadecylsulfate using tristearin as your organic starting material.

26−13 Which of the following chemical reactions could be used to distinguish between a polyunsaturated vegetable oil and a petroleum oil containing a mixture of saturated and unsaturated hydrocarbons? Explain your reasoning.

(a) addition of bromine in CCl_4 (b) hydrogenation (c) saponification (d) ozonolysis

26−14 How would you use simple chemical tests to distinguish between the following pairs of compounds?

(a) sodium stearate and *p*-dodecylbenzenesulfonate (b) beeswax and "paraffin wax"
(c) trimyristin and myristic acid (d) trimyristin and triolein

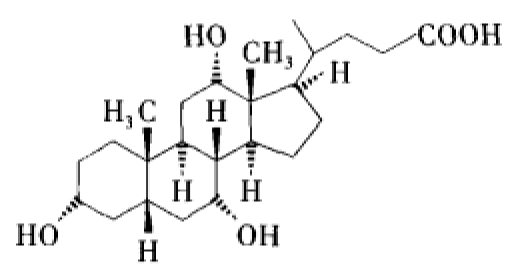
26−15 A triglyceride can be optically active if it contains two or more different fatty acids.

(a) Draw the structure of an optically active triglyceride containing one equivalent of myristic acid and two equivalents of oleic acid.
(b) Draw the structure of an optically inactive triglyceride with the same fatty acid composition.

26−16 Draw the structure of an optically active triglyceride containing one equivalent of stearic acid and two equivalents of oleic acid. Draw the products expected when this triglyceride reacts with the following reagents. In each case, predict whether the products will be optically active.

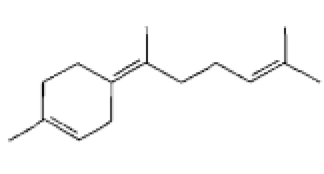
(a) H_2 and a nickel catalyst (b) Br_2 in CCl_4 (c) hot aqueous NaOH (d) ozone followed by $(CH_3)_2S$

26−17 Cholic acid, a major constituent of bile, has the following structure.

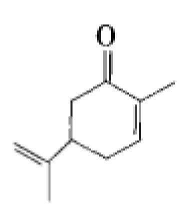


(a) Draw the structure of cholic acid showing the rings in their chair conformations, and label each methyl group and hydroxyl group as axial or equatorial. (Making a model may be helpful.)
(b) Cholic acid is secreted in bile as an amide linked to the amino group of glycine. This cholic acid-amino acid combination acts as an emulsifying agent to disperse lipids in the intestines for easier digestion. Draw the structure of the cholic acid-glycine combination, and explain why it is a good emulsifying agent.

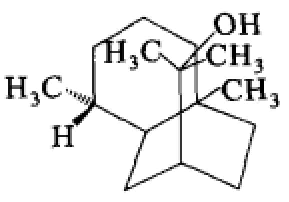
26−18 Carefully circle the isoprene units in the following terpenes, and label each compound as a monoterpene, sesquiterpene, or diterpene.

(a) 

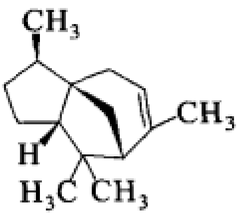
γ-bisabolene

(b) 

carvone

(c) 

patchouli alcohol

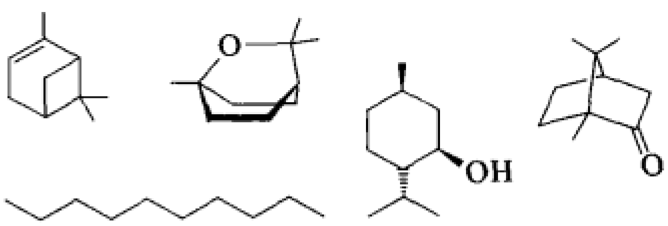
(d) 

cedrene

26−19 The following five compounds are found in Vicks Vapo-Rub®.

(a) Which are terpenes? Circle the isoprene units of the terpenes.

(b) Do you expect Vicks Vapo-Rub to be optically active? Explain.

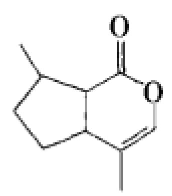


26−20 Two naturally occurring lactones are shown. For each compound, determine

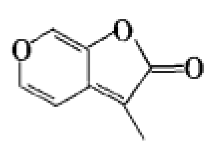
(a) whether the compound is a terpene. If so, circle the isoprene units.

(b) whether the compound is aromatic, and explain your reasoning.

(c) Show the product resulting from saponification with aqueous NaOH.



nepetalactone
the main ingredient in catnip



A compound generated in the smoke from burning plants. Promotes seed germination in plants that require fire to reproduce.

Answers to Selected Problems

These short answers are sometimes incomplete, but they should put you on the right track. Complete answers to all problems are found in the *Solutions Manual.*

CHAPTER 1

1–5. (a) $\overset{+\!\longrightarrow}{\text{C—Cl}}$; (b) $\overset{+\!\longrightarrow}{\text{C—O}}$; (c) $\overset{+\!\longrightarrow}{\text{C—N}}$; (d) $\overset{+\!\longrightarrow}{\text{C—S}}$; (e) $\overset{\longleftarrow\!+}{\text{C—B}}$; (f) $\overset{+\!\longrightarrow}{\text{N—Cl}}$; (g) $\overset{+\!\longrightarrow}{\text{N—O}}$; (h) $\overset{\longleftarrow\!+}{\text{N—S}}$; (i) $\overset{\longleftarrow\!+}{\text{N—B}}$; (j) $\overset{+\!\longrightarrow}{\text{B—Cl}}$. **1–6.** (a) +1 on O; (b) +1 on N, −1 on Cl; (c) +1 on N, −1 on Cl; (d) +1 on Na, −1 on O; (e) +1 on C; (f) −1 on C; (g) +1 on Na, −1 on B; (h) +1 on Na, −1 on B; (i) +1 on O, −1 on B; (j) +1 on N; (k) +1 on K, −1 on O; (l) +1 on O. **1–12.** (a) CH_2O, $C_3H_6O_3$; (b) $C_2H_5NO_2$, same; (c) C_2H_5Cl, same; (d) C_2H_3Cl, $C_4H_6Cl_2$. **1–13.** (a) 0.209; (b) 13.875 **1–15.** (a) favors products; (b) favors reactants; (c) favors products; (d) favors products; (e) favors products; (f) favors products. **1–18.** There is no resonance stabilization of the positive charge when the other oxygen atom is protonated. **1–22.** (a) carbon; (b) oxygen; (c) phosphorus; (d) chlorine. **1–29.** (a) different compounds; (b) resonance forms; (c) resonance forms; (d) resonance forms; (e) different compounds; (f) resonance forms; (g) resonance forms; (h) different compounds; (i) resonance forms; (j) resonance forms. **1–32.** (b) The =NH nitrogen atom is the most basic. **1–34.** (a) second; (b) first; (c) second; (d) first; (e) first. **1–39.** (a) $CH_3CH_2O^-Li^+ + CH_4$; (b) Methane; CH_3Li is a very strong base.

CHAPTER 2

2–1. sp^3; Two lone pairs compress the bond angle to 104.5°. **2–3.** Methyl carbon; sp^3, about 109.5°. Nitrile carbon sp. 180°. Nitrile nitrogen sp, no bond angle. **2–5.** The central carbon is sp, with two unhybridized p orbitals at right angles. Each terminal $=CH_2$ group must be aligned with one of these p orbitals. **2–8.** CH_3—CH=N—CH_3 shows cis-trans isomerism about the C=N double bond, but $(CH_3)_2C$=N—CH_3 has two identical substituents on the C=N carbon atom, and there are no cis-trans isomers. **2–10.** (a) cis-trans isomers; (b) constitutional isomers; (c) constitutional isomers; (d) same compound; (e) same compound; (f) same compound; (g) not isomers; (h) constitutional isomers; (i) same compound; (j) constitutional isomers; (k) constitutional isomers. **2–12.** The N—F dipole moments oppose the dipole moment of the lone pair. **2–14.** *trans* has zero dipole moment because the bond dipole moments cancel. **2–17.** (a) $CH_3CH_2OCH_2CH_3$ (b) $CH_3CH_2NHCH_3$; (c) CH_3CH_2OH; (d) CH_3COCH_3. **2–19.** No stereoisomers. **2–23.** Formamide must have an sp^2-hybridized nitrogen atom because it is involved in pi-bonding in the other resonance form. **2–27.** Only (b) and (e). **2–28.** (a) constitutional isomers; (b) constitutional isomers; (c) cis-trans isomers; (d) con-

stitutional isomers; (e) cis-trans isomers; (f) same compound; (g) cis-trans isomers; (h) constitutional isomers. **2−29.** CO_2 is *sp*-hybridized and linear; the bond dipole moments cancel. The sulfur atom in SO_2 is sp^2-hybridized and bent; the bond dipole moments do not cancel. **2−31.** Both can form H-bonds with water, but only the alcohol can form H-bonds with itself. **2−33.** (a), (c), (h), and (l) can form hydrogen bonds in the pure state. These four plus (b), (d), (g), (i), (j), and (k) can form hydrogen bonds with water.

CHAPTER 3

3−1. (a) 3-methylpentane; (b) 2-bromo-3-methylpentane; (c) 5-ethyl-2-methyl-4-propylheptane; (d) 4-isopropyl-2-methyldecane. **3−3.** (a) 2-methylbutane; (b) 2, 2-dimethylpropane; (c) 3-ethyl-2-methylhexane; (d) 2,4-dimethylhexane; (e) 3-ethyl-2, 2, 4, 5-tetramethylhexane; (f) 4-*t*-butyl-3-methylheptane. **3−6.** (a) 4-methyl-1-pentene; (b) 2-ethyl-1-hexene; (c) 1, 4-pentadiene; (d) 1, 2, 4-pentatriene; (e) 2, 5-dimethyl-1, 3-cyclopentadiene; (f) 4-vinylcyclohexene; (g) allylbenzene or 3-phenylpropene; (h) *trans*-3, 4-dimethylcyclopentene; (i) 7-methylene-1, 3, 5-cycloheptatriene. **3−10.** (a) 1, 1-dimethyl-3-(1-methylpropyl) cyclopentane or 3-*sec*-butyl-1, 1-dimethylcyclopentane; (b) 3-cyclo-propyl-1, 1-dimethylcyclohexane; (c) 4-cyclobutylnonane. **3−14.** (a) fluorobenzene; (b) 4-phenyl-1-butyne; (c) 3-methyl phenol or *m*-cresol; (d) o-nitrostyrene. **3−16.** (a) 2-phenyl-2-propanol; (b) 5-bromo-2-heptanol; (c) (*E*)-2-chloro-3-methyl-2-penten-1-ol; (d) *trans*-2-methylcyclohexanol. **3−17.** (a) 8, 8-dimethyl-2, 7-nonanediol; (b) 1, 8-octanediol; (c) *cis*-2-cyclohexene-1, 4-diol; (d) 3-cyclopentyl-2, 4-heptanediol; (e) *trans*-1, 3-cyclobutanediol. **3−19.** (a) cyclopropyl methyl ether; methoxycyclopropane; (b) ethyl isopropyl ether; 2-ethoxypropane; (c) 2-chloroethyl methyl ether; 1-chloro-2-methoxyethane; (d) 2-ethoxy-2, 3-dimethylpentane; (e) *sec*-butyl *t*-butyl ether; 2-*t*-butoxybutane. **3−20.** (a) dihydropyran; (b) 2-chloro-1, 4-dioxane; (c) 3-isopropyl pyran; (d) *trans*-2, 3-diethyloxirane or *trans*-3, 4-epoxyhexane; (e) 3-bromo-2-ethoxyfuran; (f) 3-bromo-2, 2-dimethyloxetane. **3−22.** (a) 2-pentanamine; (b) N-methyl-2-butanamine; (c) *m*-aminophenol; (d) 3-methylpyrrole; (e) *trans*-1, 2-cyclopentanediamine; (f) *cis*-4-aminocyclohexanecarbaldehyde. **3−23.** (a) 5-hydroxy-3-hexanone; ethyl β-hydroxypropyl ketone; (b) 3-phenylbutanal; β-phenylbutyraldehyde; (c) *trans*-4-methoxycy clohexanecarbaldehyde; (d) 6, 6-dimethyl-2, 4-cyclohexadienone. **3−25.** (a) 2-iodo-3-methylpentanoic acid; α-iodo-β-methylvaleric acid; (b) (*Z*)-3, 4-dimethyl-3-hexenoic acid; (c) 2, 3-dinitrobenzoic acid; (d) *trans*-1, 2-cyclohexanedicarboxylic acid; (e) 2-chlorobenzene-1, 4-dicarboxylic acid; 2-chloroterephthalic acid; (f) 3-methylhexanedioic acid; β-methyladipic acid. **3−28.** (a) 2-ethyl-1-pentene; (b) 3-ethyl-2-pentene; (c) (3*E*, 6*E*)-1, 3, 6-octatriene; (d) (*E*)-4-ethyl-3-heptene; (e) 1-cyclohexyl-1, 3-cyclohexadiene; (f) (3*Z*, 5*E*)-6-chloro-3-(chloromethyl)-1, 3, 5-octatriene. **3−29.** (b), (c), (e) and (f) show geometric isomerism. **3−33.** (a) *o*-dichlorobenzene; (b) *p*-nitroanisole; (c) 2, 3-dibromobenzoic acid; (d) *m*-chlorobenzoic acid; (e) 2, 4, 6-trichlorophenol; (f) 2-*sec*-butylbenzaldehyde. **3−34.** (a) 2-bromo-2-methylpentane; (b) 1-chloro-1-methylcyclohexane; (c) 1, 1-dichloro-3-fluorocycloheptane, (d) 4-(2-bromoethyl)-3-(fluoromethyl)-2-methylheptane; (e) 4, 4-dichloro-5-cyclopropyl-1-iodoheptane; (f) *cis*-1, 2-dichloro-1-methylcyclohexane.

CHAPTER 4

4−1. (a) hexane < octane < decane; (b) $(CH_3)_3C{-}C(CH_3)_3 < CH_3CH_2C(CH_3)_2CH_2CH_2CH_3$ < octane. **4−11.** (a) *cis*-1, 3-dimethylcyclohexane, (b) *cis*-1, 4-dimethylcyclohexane; (c) *trans*-1, 2-dimethylcyclohexane; (d) *cis*-1, 3-dimethylcyclohexane; (e) *cis*-1, 3-dimethylcyclohexane; (f) *trans*-1, 4-dimethylcyclohexane. **4−14.** (a) All except the third (isobutane) are *n*-butane. (b) Top left and bottom left are *cis*-2-butene. Top center and bottom center are 1-butene. Top right is *trans*-2-butene. Lower right is 2-methylpropene. (c)

The first and second are *cis*-1, 2-dimethylcyclopentane. The third and fourth are *trans*-1, 2-dimethylcyclopentane. The fifth is *cis*-1, 3-dimethylcyclopentane. **4−15.** (a) octane; (b) 2-methylnonane; (c) nonane. **4−19.** The trans isomer is more stable, because both of the bonds to the second cyclohexane ring are in equatorial positions.

CHAPTER 5

5−2. (a) One photon of light would be needed for every molecule of product formed (the quantum yield would be 1); (b) Methane does not absorb the visible light that initiates the reaction, and the quantum yield would. **5−3.** (a) $K_{eq} = 2.3$; (b) $[CH_3Br] = [H_2S] = 0.40$ mol/L, $[CH_3SH] = [HBr] = 0.60$ mol/L. **5−6.** (a) first order; (b) zeroth order; (c) first order overall. **5−7.** (a) zero, zero, zeroth order overall; (b) rate $= k_r$; (c) increase the surface area of the platinum catalyst. **5−8.** (c) +113 kJ/mol. **5−10.** 1°:2° ratio of 6:2, product ratio of 75% 1°and 25% 2°. **5−12.** (a) The combustion of isooctane involves highly branched, more stable tertiary free radicals that react less explosively; (b) *t*-butyl alcohol forms relatively stable alkoxy radicals that react less explosively. **5−22.** rate $= k_r[H^+][(CH_3)_3C\text{—}OH]$; second order overall. **5−23.** $PhCH_2\cdot > CH_2=CHCH_2\cdot > (CH_3)_3C\cdot > (CH_3)_2CH\cdot > CH_3CH_2\cdot > CH_3\cdot$.

CHAPTER 6

6−1. (b), (d), (e), and (f) are chiral. **6−2.** (a) achiral, no C*; (b) achiral, no C*; (c) chiral, one C*; (d) achiral, no C*; (e) achiral, no C*; (f) chiral, one C*; (g) achiral, two C*; (h) chiral, two C*; (i) achiral, no C*; (j) chiral, one C*; (k) chiral, two C*. **6−4.** (a) mirror, achiral; (b) mirror, achiral; (c) chiral, no mirror; (d) chiral, no mirror; (e) chiral, no mirror; (f) mirror, achiral; (g) mirror, achiral; (h) chiral, no mirror. **6−5.** (a) (*R*); (b) (*S*); (c) (*R*); (d) (*S*), (*S*); (e) (*R*), (*S*); (f) (*R*), (*S*); (g) (*R*), (*R*); (h) (*R*); (i) (*S*). **6−7.** +8.7°. **6−8.** Dilute the sample. If clockwise, will make less clockwise, and vice-versa. **6−9.** ee = 33.3%. Specific rotation = 33.3% of +13.5° = +4.5°. **6−12.** (a), (b), (f) and (h) are chiral; only (h) has chiral carbons. **6−14.** (a), (d), and (f) are chiral. The others have internal mirror planes. **6−15.** (a) (*R*); (b) none; (c) none; (d) (2*R*), (3*R*); (e) (2*S*), (3*R*); (f) (2*R*), (3*R*); (g) (*R*); (h) (*S*); (i) (*S*). **6−16.** (a) enantiomers; (b) diastereomers; (c) diastereomers; (d) constitutional isomers; (e) enantiomers; (f) diastereomers; (g) enantiomers; (h) same compound; (i) diastereomers. **6−19.** (a), (b), and (d) are pairs of diastereomers and could theoretically be separated by their physical properties. **6−26.** (a) same compound; (b) enantiomers; (c) enantiomers; (d) enantiomers; (e) enantiomers; (f) diastereomers; (g) enantiomers; (h) same compound. **6−29.** (b) (−) 15.90°; (c) 7.95°/15.90° = 50% ee. Composition is 75% (*R*) and 25% (*S*).

CHAPTER 7

7−2. Water is denser than hexane, so water forms the lower layer. Chloroform is denser than water, so chloroform forms the lower layer. **7−6.** 0.02 mol/L per second. **7−8.** (a) $(CH_3CH_2)_2NH$, less hindered; (b) $(CH_3)_2S$, S more polarizable; (c) PH_3, P more polarizable; (d) CH_3S^-, neg. charged; (e) $(CH_3)_3N$, N less electronegative; (f) CH_3S^-, neg. charge, more polarizable; (g) $CH_3CH_2CH_2O^-$, less hindered; (h) I^-, more polarizable. **7−10.** methyl iodide > methyl chloride > ethyl chloride > isopropyl bromide ≫ neopentyl bromide, *t*-butyl iodide. **7−16.** (a) $(CH_3)_2C(OCOCH_3)CH_2CH_3$, first order; (b) 1-methoxy-2-methylpropane, second order; (c) 1-ethoxy-1-methylcyclohexane, first order; (d) methoxycyclohexane, first order; (e) ethoxycyclohexane, second order. **7−28.** (a) 1-chlorobutane; (b) 1-iodobutane; (c) 4-chloro-2, 2-dimethyl-

pentane; (d) 1-bromo-2, 2-dimethylpentane; (e) chloromethylcyclohexane; (f) 2-methyl-1-bromopropane. **7−29.** (a) *t*-butyl chloride; (b) 2-chlorobutane; (c) bromocyclohexane; (d) iodocyclohexane; (e) *t*-butyl bromide; (f) 3-bromocyclohexene. **7−32.** (a) rate doubles; (b) rate multiplied by six; (c) rate increases. **7−39.** (a) (*R*)-2-cyanobutane (inversion); (b) (2*S*, 3*R*)-3-methyl-2-pentanol (inversion); (c) racemic mixture of 3-ethoxy-2, 3-dimethylpentanes (racemization). **7−40.** (a) diethyl ether; (b) $PhCH_2CH_2CN$; (c) $PhSCH_2CH_3$; (d) 1-dodecyne; (e) *N*-methylpyridinium iodide; (f) $(CH_3)_3CCH_2CH_2NH_2$; (g) tetrahydrofuran; (h) *cis*-4-methylcyclohexanol.

CHAPTER 8

8−2. (a) one; (b) one; (c) three; (d) four; (e) five. **8−3.** (a) *cis*-1, 2-dibromoethene; (b) *cis* (*trans* has zero dipole moment), (c) 1, 2-dichlorocyclohexene. **8−9.** There is no hydrogen *trans* to the bromide leaving group. **8−15.** In the first example the bromines are axial; in the second, equatorial. **8−18.** (a) $\Delta G > 0$, disfavored; (b) $\Delta G < 0$, favored. **8−19.** (a) strong bases and nucleophiles; (b) strong acids and electrophiles; (c) free-radical chain reaction; (d) strong acids and electrophiles. **8−23.** (a) cyclopentene; (b) 2-methyl-2-butene (major) and 2-methyl-1-butene (minor); (c) 1-methylcyclohexene (major) and methylenecyclohexane (minor); (d) 1 methylcyclohexene (minor) and methy lenecyclohexane (major). **8−26.** (a) a 1-halobutane; (b) a *t*-butyl halide; (c) a 3-halopentane; (d) a halomethylcyclohexane; (e) a 4-halocyclohexane (preferably *cis*). **8−28.** (a) 2-pentene; (b) 1-methylcyclopentene; (c) 1-methylcyclohexene; (d) 2-methyl-2-butene (rearrangement). **8−37.** E1 with rearrangement by an alkyl shift. The Zaitsev product violates Bredt's rule.

CHAPTER 9

9−2. (a) 1-bromo-2-methylpropane; (b) 1-bromo-2-methylcyclopentane; (c) 2-bromo-1-phenylpropane. **9−6.** (a) 1-methylcyclopentanol; (b) 2-phenyl-2-propanol; (c) 1-phenylcy clohexanol. **9−14.** The carbocation can be attacked from either face. **9−17.** (a) Cl_2/H_2O; (b) KOH/hear, then Cl_2/H_2O; (c) H_2SO_4/heat, then Cl_2/H_2O. **9−25.** (a) *cis*-cyclohexane-1, 2-diol; (b) *trans*-cyclohexane-1, 2-diol; (c) and (f) (*R*,*S*)-2, 3-pentanediol (+ enantiomer); (d) and (e) (*R*,*R*)-2,3-pentanediol (+ enantiomer). **9−26.** (a) OsO_4/H_2O_2; (b) CH_3CO_3H/H_3O^+, (c) CH_3CO_3H/H_3O^+; (d) OsO_4/H_2O_2. **9−36.** (a) 1-methylcyclohexene, RCO_3H/H_3O^+; (b) cyclooctene, OsO_4/H_2O_2; (c) *trans*-cyclodecene, Br_2; (d) cyclohexene, Cl_2/H_2O.

CHAPTER 10

10−1. decomposition to its elements, C and H_2. **10−2.** Treat the mixture with $NaNH_2$ to remove the 1-hexyne. **10−3.** (a) $Na^{+-}C{\equiv}CH$ and NH_3; (b) $Li^{+-}C{\equiv}CH$ and CH_4; (c) no reaction; (d) no reaction; (e) acetylene + $NaOCH_3$; (f) acetylene + NaOH; (g) no reaction; (h) no reaction; (i) NH_3 + $NaOCH_3$. **10−4.** (a) $NaNH_2$; butyl halide; (b) $NaNH_2$; propyl halide; $NaNH_2$; methyl halide. (c) $NaNH_2$; ethyl halide; repeat; (d) S_N2 on *sec*-butyl halide is unfavorable; (e) $NaNH_2$; isobutyl halide (low yield); $NaNH_2$; methyl halide; (f) $NaNH_2$ added for second substitution on 1, 8-dibromooctane might attack the halide. **10−5.** (a) sodium acetylide + formaldehyde; (b) sodium acetylide + $PhCOCH_3$; (c) sodium acetylide + CH_3I, then $NaNH_2$, then $CH_3CH_2CH_2CHO$; (d) sodium acetylide + CH_3I, then $NaNH_2$, then $CH_3CH_2COCH_3$. **10−9.** (a) H_2, Lindlar; (b) Na, NH_3; (c), (d) Add halogen, dehydrohalogenate to the alkyne, reduce as needed. **10−11.** (a) $CH_3CCl_2CH_2C_5H_{11}$ and $CH_3CH_2CCl_2C_5H_{11}$; (b) Lone pairs on Cl help stabilize the carbocation. **10−13.** (a) Cl_2; (b) HBr, peroxides; (c) HBr, no peroxides; (d) excess Br_2; (e) reduce to 1-hexene, add

HBr; (f) excess HBr. **10−15.** (a) 2-hexanone; hexanal; (b) mixtures of 2-hexanone and 3-hexanone; (c) 3-hexanone for both; (d) cyclodecanone for both. **10−17.** (a) $CH_3C{\equiv}C(CH_2)_4C{\equiv}CCH_3$ **10−24.** 1, 3-cyclohexadiene with ($HC{\equiv}C{-}CH{=}CH{-}$) at the 1 position (cis or trans).

CHAPTER 11

11−1. (a) 2, 4-hexadiene < 1, 3-hexadiene < 1, 4-hexadiene < 1, 5-hexadiene < 1, 2-hexadiene < 1, 3, 5-hexatriene; (b) third < fifth < first < fourth < second. **11−6.** 3-ethoxy-1-methylcyclopentene and 3-ethoxy-3-methylcyclopentene. **11−8.** (a) **A** is 3, 4-dibromo-1-butene; **B** is 1, 4-dibromo-2-butene; (c) Hint: **A** is the kinetic product, **B** is the thermodynamic product; (d) Isomerization to an equilibrium mixture. 10% **A** and 90% **B**. **11−9.** (a) 1-(bromomethyl) cyclohexene and 2-bromo-1-methylenecyclohexane. **11−10.** (a) 3-bromocyclopentene; (b) (*cis* and *trans*) 4-bromo-2-pentene. (c) $PhCH_2Br$ **11−17.** (b) [4 + 2] cycloaddition of one butadiene with just one of the double bonds of another butadiene. **11−19.** (a) allylcyclohexane; (b) 3-chlorocyclopentene; (c) 3-bromo-2-methylpropene; (d) 3-bromo-1-pentene and 1-bromo-2-pentene; (e) 4-bromo-2-buten-1-ol and 1-bromo-3-buten-2-ol; (f) 5, 6-dibromo-1, 3-hexadiene, 1, 6-dibromo-2, 4-hexadiene, and 3, 6-dibromo-1, 4-hexadiene (minor); (g) 1-(methoxymethyl)-2-methylcyclopentene and 1-methoxy-1-methyl-2-methylenecyclopentane; (h), (i), and (j) Diels-Alder adducts. **11−21.** 3-bromo-1-hexene, and (*cis* and *trans*)-1-bromo-2-hexene.

CHAPTER 12

12−2. 800. **12−3.** (a) 353 nm; (b) 313 nm; (c) 232 nm; (d) 273 nm; (e) 237 nm. **12−8.** Spectrum (a) is for compound E, (b) for D, and (c) for C. **12−9.** (a) 19000; (b) second structure.

CHAPTER 13

13−1. (a) three; (b) two; (c) three; (d) five. **13−2.** *trans*-$CHCl{=}CHCN$. **13−3.** (a) 1-chloropropane; (b) methyl *p*-methylbenzoate, $CH_3C_6H_4COOCH_3$. **13−4.** (a) allyl alcohol, $H_2C{=}CHCH_2OH$. **13−5.** the isobutyl cation, $(CH_3)_2CHCH_2^+$. **13−8.** 126: loss of water; 111: allylic cleavage; 87: cleavage next to alcohol. **13−9.** (a) The product isomerized, 1630 suggests conjugated; (b) 2-propyl-1, 3-cyclohexadiene. **13−11.** (a) $PhCH_2CH_2OCOCH_3$. **13−15.** 1, 1, 2-trichloropropane. **13−20.** $PhCH_2CN$.

CHAPTER 14

14−1. (a) cyclohexanol; more compact; (b) 4-methylphenol; more compact, stronger H-bonds; (c) 3-ethyl-3-hexanol; more spherical; (d) cyclooctane-1, 4-diol; more OH groups per carbon; (e) enantiomers; equal solubility. **14−3.** (a) methanol; less substituted; (b) 2-chloro-1-propanol; chlorine closer to the OH group; (c) 2, 2-dichloroethanol; two chlorines to stabilize the alkoxide; (d) 2, 2-difluoro-1-propanol; F is more electronegative than Cl, stabilizing the alkoxide. **14−5.** The anions of 2-nitrophenol and 4-nitrophenol (but not 3-nitrophenol) are stabilized by resonance with the nitro group. **14−6.** (a) The phenol (left) is deprotonated by sodium hydroxide; it dissolves. (b) In a separatory funnel, the alcohol (right) will go into an ether layer and the phenolic compound will go into an aqueous sodium hydroxide layer. **14−7.** (b), (f), (g), (h). **14−11.** (a) 3 ways: (i) $CH_3CH_2MgBr + PhCOCH_2CH_2CH_3$, (ii) $PhMgBr + CH_3CH_2COCH_2CH_2CH_3$, (iii) $CH_3CH_2CH_2MgBr + PhCOCH_2CH_3$; (b) $PhMgBr + PhCOPh$; (c) CH_3MgI + cyclohexanone; (d) $CH_3CH_2CH_2MgBr$ + dicyclohexyl ketone. **14−13.** (a) 2 $PhMgBr + PhCOCl$; (b) $2CH_3CH_2MgBr$ +

$(CH_3)_2CHCOCl$; (c) 2 c-HxMgBr + PhCOCl. **14–15.** (a) PhMgBr + ethylene oxide; (b) $(CH_3)_2CHCH_2MgBr$ + ethylene oxide; (c) 2-methylcyclohexylmagnesium bromide + ethylene oxide. **14–19.** (a) Grignard removes NH proton; (b) Grignard attacks ester; (c) Water will destroy Grignard; (d) Grignard removes OH proton. **14–22.** (a) heptanoic acid + $LiAlH_4$; or heptaldehyde + $NaBH_4$; (b) 2-heptanone + $NaBH_4$; (c) 2-methyl-3-hexanone + $NaBH_4$; (d) ketoester + $NaBH_4$. **14–26.** (a) 1-hexanol, larger surface area; (b) 2-hexanol, hydrogen-bonded; (c) 1, 5-hexanediol, two OH groups; (d) 2-hexanol. **14–30.** (a) cyclohexylmethanol; (b) 2-cyclopentyl-2-pentanol; (c) 2-methyl-1-phenyl-1-propanol; (d) methane + 3-hydroxycyclohexanone; (e) cyclopentylmethanol; (f) triphenylmethanol; (g) 1-cyclopentyl-1, 1-diphenylmethanol; (h) 5-phenyl-5-nonanol; (i) reduction of just the ketone, but not the ester; (j) 3-(2-hydroxyethyl) cyclohexanol from reduction of ketone and ester; (k) the tertiary alcohol from Markovnikov orientation of addition of H—OH; (l) the secondary alcohol from anti-Markovnikov orientation of addition of H—OH; (m) (2*S*,3*S*)-2,3-hexanediol (+ enantiomer); (n) (2*S*, 3*R*)-2,3-hexanediol (+ enantiomer); (o) 1, 4-heptadiene. **14–31.** (a) EtMgBr; (b) Grignard with formaldehyde; (c) c-HxMgBr; (d) cyclohexylmagnesium bromide with ethylene oxide; (e) PhMgBr with formaldehyde; (f) 2 CH_3MgI; (g) cyclopentylmagnesium bromide; (h) $CH_3C{\equiv}CMgX$.

CHAPTER 15

15–4. (a) PCC; (b) chromic acid; (c) chromic acid or Jones reagent; (d) PCC; (e) chromic acid; (f) dehydrate, hydroborate, oxidize (chromic acid or Jones reagent). **15–6.** Treat the tosylate with (a) bromide; (b) ammonia; (c) ethoxide; (d) cyanide. **15–8.** (a) chromic acid or Lucas reagent; (b) chromic acid or Lucas reagent; (c) Lucas reagent only; (d) Lucas reagent only; allyl alcohol forms a resonance-stabilized carbocation. (e) Lucas reagent only. **15–12.** (a) thionyl chloride (retention); (b) tosylate (retention), then S_N2 using chloride ion (inversion). **15–13.** resonance-delocalized cation, positive charge spread over two carbons. **15–15.** (a) 2-methyl-2-butene (+2-methyl-1-butene); (b) 2-pentene (+1-pentene); (c) 2-pentene (+1-pentene); (d) c-Hx $=C(CH_3)_2$ (+1-isopropylcyclohexene); (e) 1-methylcyclohexene (+3-methylcyclohexene). **15–20.** (a) the alkoxide of cyclohexanol and an ethyl halide or tosylate; (b) dehydration of cyclohexanol. **15–27.** (a) Na, then ethyl bromide; (b) NaOH, then PCC to aldehyde; Grignard, then dehydrate; (c) Mg in ether, then $CH_3CH_2CH_2CHO$, then oxidize; (d) PCC, then EtMgBr. **15–29.** (a) thionyl chloride; (b) make tosylate, displace with bromide; (c) make tosylate, displace with hydroxide. **15–34.** Compound A is 2-butanol. **15–39.** **X** is 1-buten-4-ol; **Y** is tetrahydrofuran (5-membered cyclic ether).

CHAPTER 16

16–2. $(CH_3CH_2)_2O^+\,{}^-AlCl_3$. **16–5.** Intermolecular dehydration of a mixture of methanol and ethanol would produce a mixture of diethyl ether, dimethyl ether, and ethyl methyl ether. **16–7.** Intermolecular dehydration might work for (a). Use the Williamson for (b). Alkoxymercuration is best for (c). **16–9.** (a) bromocyclohexane and ethyl bromide; (b) 1, 5-diiodopentane; (c) phenol and methyl bromide; (e) phenol, ethyl bromide, and 1, 4-dibromo-2-methylbutane. **16–14.** (a) $CH_3CH_2OCH_2CH_2O^-\,Na^+$; (b) $H_2NCH_2CH_2O^-\,Na^+$; (c) Ph—$SCH_2CH_2O^-\,Na^+$; (d) $PhNHCH_2CH_2OH$; (e) $N{\equiv}C{-}CH_2CH_2O^-\,Na^+$; (f) $N_3CH_2CH_2O^-\,Na^+$. **16–15.** (a) 2-methyl-1, 2-propanediol, ^{18}O at the C2 hydroxyl group; (b) 2-methyl-1, 2-propanediol, ^{18}O at the C1 hydroxyl group; (c), (d) same products, (*S*, *S*) and (*R*, *R*). **16–16.** (a) $(CH_3)_2CH{-}CH_2CH_2{-}OH$; (b) $CH_3CH_2C(CH_3)_2{-}OH$; (c) 1 cyclopentyl-1-butanol. **16–20.** (a) The old ether had autoxidized to form peroxides. On distillation, the peroxides were heated and concentrated, and they detonated. (b) Discard the old

ether or treat it to reduce the peroxides. **16−24.** (a) epoxide + PhMgBr; (b) epoxide + $NaOCH_3$ in methanol; (c) epoxide + methanol, H^+. **16−28.** Sodium then ethyl iodide gives retention of configuration. Tosylation gives retention, then the Williamson gives inversion. Second Product (+) 15.6°.

CHAPTER 17

17−2. (a) +31.8 kJ/mol; (b) −88.6 kJ/mol; (c) −112.0 kJ/mol. **17−5.** (a) nonaromatic (internal H's prevent planarity); (b) nonaromatic (one ring atom has no *p* orbital); (c) aromatic, [14] annulene; (d) aromatic (in the outer system). **17−6.** Azulene is aromatic, but the other two are antiaromatic. **17−7.** (a) antiaromatic if planar; (b) aromatic if planar; (c) aromatic if planar; (d) antiaromatic if planar; (e) nonaromatic; (f) aromatic if planar. **17−10.** (a) aromatic; (b) aromatic; (c) nonaromatic; (d) aromatic; (e) aromatic; (f) nonaromatic; (g) aromatic. **17−12.** second is deprotonated to an aromatic cyclopentadienyl anion. **17−17.** (a) three; (b) one; (c) *meta*-dibromobenzene.

CHAPTER 18

18−3. Strong acid is used for nitration, and the amino group of aniline is protonated to a deactivating $—NH_3^+$ group. **18−6.** (a) *t*-butylbenzene; (b) 2-and 4-*sec*-butyltoluene; (c) no reaction; (d) (1,1,2-trimethylpropyl) benzene. **18−7.** (a) *sec*-butylbenzene and others; (b) OK; (c) + disub, trisub; (d) OK (some ortho); (e) OK. **18−9.** (a) $(CH_3)_2CHCH_2COCl$, benzene, $AlCl_3$; (b) $(CH_3)_3CCOCl$, benzene, $AlCl_3$; (c) PhCOCl, benzene, $AlCl_3$; (d) CO/HCl, $AlCl_3$/CuCl, anisole; (e) Clemmensen on (b); (f) $CH_3(CH_2)_2COCl$, benzene, $AlCl_3$ then Clemmensen. **18−11.** (a) 2,4-dinitroanisole; (b) 2,4-and 3,5-dimethylphenol; (c) *N*-methyl-4-nitroaniline; (d) 2,4-dinitrophenylhydrazine. **18−13.** (a) 1-bromo-1-phenylpropane. **18−15.** (a) HBr, then Grignard with ethylene oxide; (b) CH_3COCl and $AlCl_3$, then Clemmensen, Br_2 and light, then $^-OCH_3$; (c) nitrate, then Br_2 and light, then NaCN. **18−16.** (a) 3-ethoxytoluene; (b) *m*-tolyl acetate; (c) 2,4,6-tribromo-3-methylphenol; (d) 2,4,6-tribromo-3-(tribromomethyl) phenol; (e) 2-methyl-1,4-benzoquinone; (f) 2,4-di-*t*-butyl-3-methyl-phenol. **18−29.** The yellow species is the triphenylmethylcation. **18−34.** kinetic control at 0°, thermodynamic control at 100°. **18−35.** Brominate, then Grignard with 2-butanone.

CHAPTER 19

19−3. (a) 3-heptanone; (b) phenylacet onitrile; (c) benzyl cyclopentyl ketone. **19−5.** (a) benzyl alcohol; (b) benzaldehyde; (c) 3-butyl-1,4-pentadien-3-ol; (d) 1-hepten-3-one. **19−8.** second < fourth < first < third. **19−11.** (a) tetralone and ethanol; (b) acetaldehyde and 2-propanol; (c) hexane-2,4-dione and ethanediol; (d) tetralone and 1,3-propanediol; (e) 5-hydroxypentanal and cyclohexanol; (f) $(HOCH_2CH_2CH_2)_2CHCHO$. **19−17.** *Z* and *E* isomers. **19−18.** (a) cyclohexanone and methylamine; (b) 2-butanone and ammonia; (c) acetaldehyde and aniline; (d) 6-amino-2-hexanone **19−22.** $[(CH_3)_3P—R]^+$ could lose a proton from a CH_3. **19−24.** (a) Wittig of $PhCH_2Br$ + acetone; (b) Wittig of CH_3I + $PhCOCH_3$; (c) Wittig of $PhCH_2Br$ + PhCH=CHCHO; (d) Wittig of CH_3I + cyclopentanone; (e) Wittig of EtBr + cyclohexanone. **19−25.** (a) 4-hydroxycyclohexanecarboxylic acid; (b) 4-oxocyclohexanecarboxylic acid; (c) 3-oxocyclohexanecarboxylic acid; (d) *cis*-3,4-dihydroxycyclohexanecarboxylic acid. **19−26.** (a) indane; (b) hexane; (c) ethylene ketal of 2-propylcyclohexanone; (d) propylcyclohexane. **19−29.** 2,5-hexanedione **19−34.** (all H^+ cat.) (a) cyclobutanone and hydroxylamine; (b) benzaldehyde and cyclopentylamine; (c) benzylamine and cyclopentanone; (d) β-tetralone and ethylene glycol; (e) cyclohexylamine and acetone; (f)

cyclopentanone and methanol. **19–37.** (a) $NaBD_4$, then H_2O; (b) $NaBD_4$, then D_2O; (c) $NaBH_4$, then D_2O. **19–40.** $CH_3CH_2CH_2COCl$ and $AlCl_3$, then Clemmensen; (b) EtMgBr, then H_3O^+; (c) $Cl_2/FeCl_3$, then Dow process to phenol; NaOH, CH_3I, then Gatterman; (d) oxidize to the acid, $SOCl_2$, then $AlCl_3$. **19–44.** (a) 3-hexanone; (b) 2-and 3-hexanone; (c) 2-hexanone; (d) cyclodecanone; (e) 2-and 3-methylcyclodecanone. **19–46.** **A** is 2-heptanone. **19–49.** (b) The "THP ether" is an acetal, stable to base but hydrolyzed by acid.

CHAPTER 20

20–1. (a) resolvable (chiral carbons); (b) not resolvable (N inverts); (c) symmetric; (d) not resolvable; proton on N is removable; (e) resolvable (chiral quat. salt). **20–3.** (a) aniline < ammonia < methylamine < NaOH; (b) *p*-nitroaniline < aniline < *p*-methylaniline; (c) pyrrole < aniline < pyridine; (d) 3-nitropyrrole < pyrrole < imidazole. **20–7.** (a) benzylamine + excess CH_3I; (b) 1-bromopentane + excess NH_3; (c) benzyl bromide + excess NH_3. **20–11.** (a) cyclohexanediazonium chloride (then cyclohexanol and cyclohexene); (b) *N*-nitroso-*N*-ethyl-2-hexanamine; (c) *N*-nitrosopiperidine; (d) benzenediazonium chloride. **20–13.** (a) diazotize, then HBF_4, heat; (b) diazotize, then CuCl; (c) protect (CH_3COCl), then 3 $CH_3I/AlCl_3$, H_3O^+, diazotize, H_3PO_2; (d) diazotize, then CuBr; (e) diazotize, then KI; (f) diazotize, then CuCN; (g) diazotize, then H_2SO_4, H_2O, heat; (h) diazotize, then couple with resorcinol. **20–14.** (a) CH_3NH_2, $Na(AcO)_3BH$; (b) H_2NOH/H^+ then $LiAlH_4$; (c) PhCHO, $Na(AcO)_3BH$; (d) aniline/H^+, then $LiAlH_4$; (e) H_2NOH/H^+, then $LiAlH_4$; (f) piperidine + cyclopentanone + $Na(AcO)_3BH$. **20–18.** (a) nitrate, reduce; (b) brominate, then nitrate and reduce; (c) nitrate, then brominate and reduce; (d) oxidize toluene, then nitrate and reduce. **20–22.** only (b), (d), (f), and (h). **20–24.** (a) 2-phenylethylamine; (b) 1,4-butanediamine; (c) *trans*-2-phenylcyclopropanamine. **20–36.** (a) triethylamine; (b) An acid converts it to a solid ammonium salt; (c) Rinse the clothes with diluted vinegar (acetic acid).

CHAPTER 21

21–1. (a) first, second, third; (b) third, second, first; (c) third, second, fourth, first. **21–5.** (a) $KMnO_4$; (b) $KMnO_4$; (c) PhMgBr + ethylene oxide, oxidize; (d) PBr_3, Grignard, CO_2; (e) conc. $KMnO_4$, heat; (f) KCN, then H_3O^+. **21–8.** (a) methanol and salicylic acid, H^+; methanol solvent, dehydrating agent; (b) methanol and formic acid H^+, distill product as it forms; (c) ethanol and benzoic acid, H^+, ethanol solvent, dehydrating agent. **21–9.** (a) see Fischer esterification; (b) $C—^{18}O—CH_3$; (c) mass spectrometry. **21–10.** (a) benzene + CH_3CH_2COCl, $AlCl_3$; or propionic acid + 2 PhLi, then H_3O^+; (b) Add 2 CH_3Li, then H_3O^+. **21–19.** (a) Grignard + CO_2; or KCN, then H_3O^+; (b) conc. $KMnO_4$, heat; (c) Ag^+; (d) $SOCl_2$, then Li(*t*-BuO)$_3$AlH; or $LiAlH_4$, then PCC; (e) CH_3OH, H^+; or CH_2N_2; (f) $LiAlH_4$ or B_2H_6; (g) $SOCl_2$, then excess CH_3NH_2. **21–21.** diastereomers **21–29.** (A) 2-phenylpropanoic acid; (B) 2-methylpropenoic acid; (C) *trans*-2-hexenoic acid.

CHAPTER 22

22–3. (a) ethanol, propionyl chloride; (b) phenol, 3-methylhexanoyl chloride; (c) benzyl alcohol, benzoyl chloride; (d) cyclopropanol, cyclohexanecarbonyl chloride; (e) *t*-butyl alcohol, acetyl chloride; (f) allyl alcohol, succinoyl chloride. **22–4.** (a) dimethylamine, acetyl chloride; (b) aniline, acetyl chloride; (c) ammonia, cyclohexanecarbonyl chloride; (d) piperidine, benzoyl chloride. **22–5.** (i) $PhCH_2OH$; (ii) Et_2NH.

22-14. (a) ethyl benzoate; (b) acetic benzoic anhydride; (c) PhCONHPh; (d) 4-methoxybenzophenone; (e) Ph_3COH; (f) benzaldehyde. **22-17.** (a) acetic formic anhydride; (b) $SOCl_2$, then CH_3COONa; (c) oxalyl chloride; (d) H^+ and heat to form anhydride, then one equivalent of $(CH_3)_2CHOH$; (e) oxidize aldehyde with Ag^+, then form lactone with H^+; (f) $NaBH_4$ to reduce aldehyde, then H^+ to form lactone. **22-20.** (after H^+) (a) HCOOH + PhOH; (b) $CH_3CH_2COOH + CH_3CH_2OH$; (c) 3-(*o*-hydroxyphenyl)-propanoic acid; (d) $(CH_2OH)_2 + (COOH)_2$ **22-24.** (a) Ph_3COH; (b) 3 EtMgBr + EtCOOEt, then H_3O^+. **22-27.** (a) diethyl carbonate; (b) $CH_3NHCONHCH_3$; (c) $CH_3OCONHPh$. **22-31.** Penicillin **22-33.** A is hexanenitrile; B is hexanamide. **22-34.** Acetic anhydride; add water to hydrolyze it to dilute acetic acid.

CHAPTER 23

23-6. (a), (b) cyclopentanecarboxylate and chloroform/iodoform; (c) $PhCOCBr_2CH_3$. **23-10.** (a) enamine + allyl bromide; (b) *enamine* + $PhCH_2Br$; (c) *enamine* + PhCOCl. **23-11.** retro-aldol, reverse of aldol condensation. **23-13.** no second alpha proton to form the final enolate to drive the reaction to completion. **23-14.** (a) methyl 2-methyl-3-oxopentanoate; (b) ethyl 2, 4-diphenyl-3-oxobutanoate. **23-17.** (a) PhCOOEt + CH_3CH_2COOEt; (b) $PhCH_2COOMe$ + MeOCOCOOMe; (c) $(EtO)_2C{=}O + PhCH_2COOEt$; (d) $(CH_3)_3CCOOMe + CH_3(CH_2)_3COOMe$. **23-19.** Alkylate malonic ester with: (a) $PhCH_2Br$; (b) CH_3I (twice); (c) $PhCH_2CH_2Br$; (d) $Br(CH_2)_4Br$ (twice). **23-20.** Alky late acetoacetic ester with: (a) $PhCH_2Br$; (b) $Br(CH_2)_4Br$(twice); (c) $PhCH_2Br$, then $CH_2{=}CHCH_2Br$ **23-21.** Alkylate the enamine of cyclohexanone with MVK. **23-22.** (a) malonic ester anion + ethyl cinnamate; (b) malonic ester anion + acrylonitrile, then H_3O^+ (c) enamine of cyclopentanone + acrylonitrile, then H_3O^+; (d) enamine of 2-methylcyclopentanone + $PhCOCH{=}CH_2$, then H_3O^+; (e) alkylate acetoacetic ester with CH_3I, *then* MVK, *then* H_3O^+; (f) hydrolyze the product from (a) **23-27.** (1) g < b < f < a < c < d < e; (2) a, c, d, e. **23-35.** Alkylate with: (a) $PhCH_2Br$; (b) CH_3CH_2Br, *then* (bromomethyl) cyclopentane; (c) $Br(CH_2)_5Br$, alkylate on each end to make a cyclohexane ring. **23-36.** Alkylate with: (a) CH_3CH_2Br, then $PhCH_2Br$; (b) $Br(CH_2)_4Br$; (c) MVK (hydrolysis, decarboxylation, then Aldol gives product). **23-43.** (a) Dieckmann of dimethyl adipate, alkylation by allyl bromide, hydrolysis and decarboxylation; (b) Robinson with $CH_3CH{=}CHCOCH_3$, then reduction; (c) form enamine or enolate, acylate with ClCOOEt, methylate with CH_3I, do aldol with benzaldehyde.

CHAPTER 24

24-2. (a) two C*, two pairs of enantiomers; (b) one C*, one pair of enantiomers; (c) four C*, eight pairs of enantiomers; three C*, four pairs of enantiomers. **24-5.** (*R*) for D series, (*S*) for L series. **24-10.** Galactitol is symmetrical (meso) and achiral. **24-11.** L-gulose has the same structure as D-glucose, but with the CHO and CH_2OH ends interchanged. **24-12.** (a) non-reducing; (b) reducing; (c) reducing; (d) nonreducing; (e) reducing; (f) "sucrose" is nonreducing; should have "-oside" ending. **24-15.** **A** = D-galactose; **B** = D-talose; **C** = D-lyxose; **D** = D-threose **24-16.** **E** = D-ribose; **F** = D-erythrose. **24-20.** reducing and mutarotating. **24-21.** Trehalose is α-D-glucopyranosyl-α-D-glucopyranoside. **24-28.** (a) D-ribose; (b) D-altrose; (c) L-erythrose; (d) L-galactose; (e) L-idose. **24-35.** (a) D-arabinose and D-lyxose; (b) D-threose; (c) **X** = D-galactose; (d) No, the optically active hexose is degraded to an optically active pentose that is oxidized to an optically active aldaric acid; (e) D-threose gives an optically active aldaric acid. **24-38.** (a) D-tagatose is a ketohexose, the C4 epimer of D-fructose; (b) A pyranose with the anomeric carbon (C2) bonded to the oxygen atom of C6. **24-43.** (a) no; (b) yes; (c) Only applies to double stranded DNA.

CHAPTER 25

25−6. *N*-phthalimidomalonic ester and (a) $(CH_3)_2CHBr$; (b) $PhCH_2Br$; (c) $BrCH_2CH_2COO^-$; (d) $(CH_3)_2CHCH_2Br$. **25−13.** Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly·NH_2. **25−15.** Add ethyl chloroformate, then Gly, ethyl chloroformate, then Leu. Deprotect using H_2 and Pd. **25−17.** Add TFA (CF_3COOH), then Boc-Gly and DCC, then TFA, then Boc-Leu and DCC, then HF. **25−21.** (a) Ruhemann's purple; (b) alanine; (c) $CH_3CONH(CH_2)_4CH(COOH)$ $NHCOCH_3$; (d) L-proline and *N*-acetyl-D-proline; (e) $CH_3CH_2CH(CH_3)$ $CH(NH_2)CN$; (f) isoleucine; (g) 2-bromo-4-methylpentanoic acid (after water work-up); (h) 2-amino-4-methylpentanoic acid or leucine. **25−22.** (a) $NH_3/H_2/Pd$; (b) Br_2/PBr_3, H_2O, excess NH_3; (c) $NH_3/HCN/H_2O$, H_3O^+; (d) Gabriel-malonic ester synthesis. **25−24.** Convert the alcohol to a tosylate and displace with excess ammonia. **25−29.** aspartylphenylalanine methyl ester. **25−30.** Phe-Ala-Gly-Met-Ala. **25−33.** (a) C-terminal amide ($CONH_2$), or amide (Gln) of Glu, (b) The N-terminal Glu is a cyclic amide (a "pyroglutamyl" group) that effectively blocks the N-terminus. The C-terminal Pro is an amide; (c) cyclic pentapeptide. **25−36.** Ornithine is $H_2N(CH_2)_3CH(NH_2)COOH$, a homolog of lysine, with a similar IEP. **25−38.** Ala-Lys-Phe-Glu-Gly-Tyr-Arg-Ser-Leu-Ile.

CHAPTER 26

26−1. Hydrogenation of triolein (mp −4 ℃) gives tristearin (mp 72 ℃). **26−6.** (a) sesquiterpene; (b) monoterpene; (c) monoterpene; (d) sesquiterpene. **26−8.** (a) a triglyceride (a fat); (b) an alkyl sulfate detergent; (c) a wax; (d) a sesquiterpene; (e) a steroid. **26−10.** (a) H_2/Ni, $LiAlH_4$; (b) H_2/Ni; (c) stearic acid from (b), add $SOCl_2$, then 1-octadecanol (a); (d) O_3, then $(CH_3)_2S$; (e) $KMnO_4$, then H^+; (f) Br_2/PBr_3, then H_2O. **26−12.** reduce ($LiAlH_4$), esterify with sulfuric acid. **26−14.** (a) Sodium stearate precipitates in dilute acid or Ca^{2+}; (b) Paraffin "wax" does not saponify; (c) Myristic acid shows acidic properties when treated with base; (d) Trolein decolorizes Br_2 in CCl_4.

Index

Note: Compound names are listed by their root names, not their italicized prefixes.

Vocabulary

英文	中文	英文	中文
	A		
abietic acid	松香酸	acidic hydrolysis	酸性水解
absorption spectroscopy	吸收光谱	activating group	活化基团
abundance	丰度	activation energy	活化能
acetal	缩醛	acylation-reduction	酰化还原反应
acetaldehyde	乙醛	acyl chloride	酰氯
acetamide	乙酰胺	acyl halide	酰卤
acetamidodeoxyglucose	乙酰氨基脱氧葡萄糖	acylium ion	酰基离子
acetanilide	乙酰苯胺	adenine	腺嘌呤
acetate ion	醋酸离子	adenosine	腺苷
acetic acid	醋酸	adenosine triphosphate(ATP)	腺苷三磷酸
acetic anhydride	乙酸酐	adenylic acid	腺苷酸
acetone	丙酮	adipic acid	己二酸(肥酸)
acetonitrile	乙腈	adrenal medulla	肾上腺髓质
acetophenone	苯乙酮	aglycone	糖苷配基
acetyl	乙酰基	alanine	丙氨酸
acetylacetone	乙酰丙酮	alanyl	丙氨酰
acetyl chloride	乙酰氯	albumin	白蛋白
acetylene	乙炔	aldaric acid	醛糖二酸
N-acetylglucosamine	*N*-乙酰基葡萄糖胺	aldohexose	己醛糖
acetylide	乙炔化物	aldol condensation	羟醛缩合
acetylide ion	乙炔基阴离子	aldol product	羟醛产物
acetylsalicylic acid	乙酰水杨酸	aldonic acid	醛糖酸
(aspirin)	(阿司匹林)	aldose	醛糖
acid anhydride	酸酐	aldotetrose	丁醛糖
acid chloride	酰氯	aliphatic	脂肪族的
acid-dissociation constant	酸解离常数	alkaline	碱的,碱性的
acid halide	酰卤	alkalinity	碱度

alkaloid 生物碱
alkanediazonium cation 烷基重氮正离子
alkenyne 烯炔
alkoxide 醇盐,烷氧基负离子
alkoxyl 烷氧基
alkoxymercuration 烷氧汞化反应
alkoxymercuration-demercuration 烷氧汞化脱汞
alkyl 烷基
alkylation 烷基化
alkylbenzene 烷基苯
alkyl halide 烷基卤化物
alkynol 炔醇
allene 丙二烯
allose 阿洛糖
allyl 烯丙基
allylic cation 烯丙基阳离子
allylic radical 烯丙基自由基
allylmagnesium bromide 烯丙基溴合镁
altrose 阿卓糖
amide 酰胺
amide ion 氨基离子
amine 胺
amine oxide 氧化胺
amino acid 氨基酸
amino sugar 氨基糖
ammonia 氨,氨水
ammonium cyanate 氰酸铵
ammonium salt 铵盐
ammonolysis 氨解
amphoteric 两性的
amylopectin 支链淀粉
amylose 直链淀粉,多糖
anabolic steroid 合成代谢类固醇
an ammonium carboxylate salt 羧酸铵盐
androstane 雄(甾)烷
androsterone 雄(甾)酮
angle strain 角张力
anilide 酰替苯胺
aniline 苯胺
anilinium ion 苯铵离子
anionic polymerization 阴离子聚合
anisole 苯甲醚(茴香醚)
annulation 环化
annulene 轮烯
anomer 端基差向异构体
anthracene 蒽
antiaromatic compound 反芳香性化合物
antibonding molecular orbital 反键分子轨道
anti-coplanar 反式共面的
arabinose 阿拉伯糖
arachidic acid 花生酸
arachidonic acid 花生四烯酸
arene 芳烃
arginine 精氨酸
aromatic 芳香性的
aryl 芳基
aryl halide 芳基卤化物
ascorbic acid 抗坏血酸,维生素 C
asparagine 天冬酰胺
aspartic acid 天冬氨酸
asphalt 沥青
asymmetric carbon atom 不对称碳原子
asymmetric induction 不对称诱导
atomic orbital 原子轨道
aufbau principle 构造原理
auxochrome 助色团
azeotrope 共沸物
azide 叠氮化物
aziridine 氮杂环丙烷
azo compound 偶氮化合物
azo dye 偶氮染料
azulene 薁

B

barium sulfate 硫酸钡
base-dissociation constant 碱解离常数
basic hydrolysis 碱性水解
basicity 碱度
bathochromic shift 红移
beclomethasone 氯地米松
beef fat 牛脂,牛油
benzaldehyde 苯甲醛(安息香醛)
benzaldehyde hydrazone 苯甲醛腙
benzaldehyde methyl imine 苯甲醛甲基亚胺

benzamide 苯甲酰胺
benzenesulfonic acid 苯磺酸
benzenethiol 苯硫酚
benzenethiolate 苯硫酚盐阴离子
benzimidazole 苯并咪唑
benzopyrene 苯并芘
benzocaine 对氨基苯甲酸乙酯
benzofuran 苯并呋喃
benzoic acid 苯甲酸（安息香酸）
benzonitrile 苯甲腈
benzophenone 二苯酮
benzophenone imine 二苯酮亚胺
benzoquinone 苯醌
benzothiophene 苯并噻吩
benzyl 苄基
benzyl alcohol 苯甲醇
benzyl bromide 苄溴
benzyl chloroformate 氯甲酸苄酯
benzylic carbon 苄基碳
benzyloxycarbonyl alanine 苄氧羰基丙氨酸
benzyne 苯炔
betaine 内盐
BINAP ligand 2,2′-双二苯基膦基-1,1′-联萘配体
biphenol A 双酚 A
biphenyl 联苯
bomb calorimeter 爆炸量热器
bond-dissociation energy 键解离能
bonding molecular orbital 成键分子轨道
borane 硼烷
boron trifluoride 三氟化硼
boron trifluoride etherate 三氟化硼乙醚络合物
bovine insulin 牛胰岛素
branched alkane 支链烷烃
bridged bicyclic compound 桥联双环化合物
bromination 溴化
bromo- 溴代
bromohydrin 溴代醇
bromonium ion 溴鎓离子
N-bromosuccinimide（NBS） *N*-溴代丁二酰亚胺
butanoyl 丁酰基
butenedioic acid 丁烯二酸
butoxide ion 丁氧基离子
n-butyllithium 正丁基锂
butylmagnesium bromide 丁基溴合镁
butyraldehyde 丁醛
butyric acid 丁酸
butyronitrile 丁腈

C

cadaverine 尸胺
calcium carbide 电石
calcium oxide 氧化钙
camphor 莰酮（樟脑）
camphoraceous 樟脑特有的
canola oil 低芥酸菜籽油
capillin 毛蒿素
caraway oil 藏茴香油
carbamate 氨基甲酸酯
carbamic acid 氨基甲酸
carbanion 碳负离子
carbene 卡宾
carbenoid 类卡宾
carbinolamine 醇胺
carbinol carbon atom 醇碳原子
carbocation 碳正离子
carbohydrate 糖类
carbolic acid 石炭酸
carbonate ester 碳酸酯
carbonic acid 碳酸
carbon monoxide 一氧化碳
carbon nanotube 碳纳米管
carbon tetrahalide 四卤化碳
carbonyl 羰基
carboxylate anion 羧酸盐阴离子
carboxyl 羧基
carboxylic acid 羧酸
carboxypeptidase 羧肽酶
carnauba wax 巴西棕榈蜡
carotene 胡萝卜素
carvone 香芹酮
catalytic cracking 催化裂化

catalytic hydrogenation	催化氢化	condensation	缩合
cationic polymerization	阳离子催化聚合	condensed structure formula	缩简构造式
cedar leaf oil	雪松叶油	configuration	构型
cellobiose	纤维二糖	conformation	构象
cellulose	纤维素	conformer(conformational isomer)	构象异构体
cellulose acetate	醋酸纤维素		
cephalins	脑磷脂	conjugate acid and base	共轭酸碱
cephalosporin antibiotics	头孢菌素类抗生素	conjugate addition	共轭加成
cerebrospinal fluid	脑脊髓液	conjugated system	共轭体系
chain reaction	链式反应	constitutional isomer	构造异构体
chair-chair interconversion	椅型-椅型互变	cortisol	可的松
chair conformation	椅型构象	coupling constant	偶合常数
chemical shift	化学位移	covalent bond	共价键
chiral	手性的	cresol	甲苯酚
chirality	手性	crossed aldol condensation	交叉羟醛缩合
chitin	甲壳质	crotonic acid	巴豆酸
chloral hydrate	三氯乙醛水合物	crown ether	冠醚
chlordane	氯丹	cryogenic	低温学的
chlorination	氯化,氯化反应	cumulated double bond	累积双键
chloro-	氯代	cuprous iodide	碘化亚铜
chloroform	氯仿	cyanic acid	氢氰酸
chlorohydrin	氯乙醇	cyanide	氰化物
chloronium ion	氯鎓离子	cyano	氰基
m-chloroperoxybenzoic acid	间氯过氧化苯甲酸	cyanohydrin	氰醇化合物
chlorosulfite ester	氯代亚硫酸酯	cyclic compound	环状化合物
cholesterol	胆固醇	cycloaddition	环加成
choline	胆碱	cycloalkane	环烷烃
chromatography	色谱法,层析	cyclohexanone dimethy acetal	环己酮缩二甲醇
chromic acid	铬酸	cyclohexanone imine	环己酮亚胺
chromium trioxide	三氧化铬	cyclohexanone phenylhydrazone	环己酮苯腙
chromophore	发色团	cyclohexyllithium	环己基锂
cicutoxin	毒芹素	cyclopentadienyl	环戊二烯基
cinnamaldehyde	肉桂醛	cyclopentanone phenyl imine	环戊酮苯基亚胺
cinnamic acid	肉桂酸	cysteic acid	磺基丙氨酸
cinnamon	肉桂	cysteic acid phenylthiohydantoin	磺基丙氨酸乙内酰苯硫脲
cis-trans isomer	顺反异构体		
cocaine	可卡因	cysteine	半胱氨酸
cocaine hydrochloride	可卡因盐酸盐	cytidine	胞(嘧啶核)苷
cochineal	胭脂红	cytidylic acid	胞苷酸
coenzyme	辅酶	cytochrome	细胞色素
concerted reaction	协同反应	cytosine	胞嘧啶

D

dacron polyester fiber 涤纶聚酯纤维
deoxyribofuranose 呋喃脱氧核糖
deactivating group 钝化基团
deamination 脱氨基作用
debromination 脱溴作用,脱溴反应
decalin 十氢化萘
decarboxylate 脱羧产物
degenerate orbital 简并轨道
degradation 降解
degree of unsaturation 不饱和度
dehalogenation 脱卤作用,脱卤反应
dehydrating agent 脱水剂
dehydration 脱水
dehydrogenation 脱氢作用,脱氢反应
dehydrohalogenation 脱卤化氢(作用)
delocalized 离域的,非定域的
denaturation 变性(剂)
deoxyadenosine 腺嘌呤脱氧核苷
deoxycytidine 胞嘧啶脱氧核苷
deoxygenation 脱氧反应
deoxyguanosine 鸟嘌呤脱氧核苷
deoxyribonucleic acid (DNA) 脱氧核糖核酸
deoxyribonucleoside 脱氧核糖核苷
deoxyribose 脱氧核糖
deoxythymidine 胸腺嘧啶脱氧核苷
deprotonation 脱质子化作用
deshielding effect 去屏蔽效应
desulfonation 去磺化
dextrorotatory 右旋性的
dextrose 右旋糖
diacetone alcohol 双丙酮醇
diastereomer 非对映异构体
diazo coupling 重氮偶合
diazomethane 重氮甲烷
diazonium salt 重氮盐
diazotization 重氮化
dibenzopyrene 二苯并芘
diborane(B_2H_6) 乙硼烷
dicyclohexylcarbodiimide(DCC) 二环己基碳二亚胺
dielectric constant 介电常数
diene 二烯烃
dienophile 二烯亲和物
diethanolamine 二乙醇胺
diethyl adipate 己二酸二乙酯
diethyl carbonate 碳酸二乙酯
diethyl malonate 丙二酸二乙酯
dihedral angle 二面角
dihydropyran 二氢吡喃
diketone 二酮
dimercaprol 2,3-二巯基-1-丙醇
dimethoxyethane 二甲氧基乙烷
N,*N*-dimethylacetamide *N*,*N*-二甲基乙酰胺
dimethyl carbonate 碳酸二甲酯
dimethylformamide 二甲基甲酰胺
dimethyl oxalate 草酸二甲酯
dimethyl phthalate 邻苯二甲酸二甲酯
dimethyl pimelate 庚二酸二甲酯
dimethyl sulfate 硫酸二甲酯
dimethyl sulfoxide 二甲基亚砜
diol 二醇
dioxane 二氧六环
dipolar ion (zwitterion) 两性离子
dipole-dipole force 偶极-偶极作用
dipole moment 偶极矩
disaccharide 二糖;双糖
di(secondary isoamyl)borane 二(仲异戊基)硼烷
distillation 蒸馏
di-*t*-butyldicarbonate 二叔丁基焦碳酸酯
diterpene 双萜
dithiane 二噻烷
dopamine 多巴胺
double bond 双键
doublet 双重峰

E

eclipsed conformation 重叠构象
electromagnetic spectrum 电磁谱

electronegativity 电负性
electronic configuration 电子构型
electron impact ionization 电子轰击电离
electron-withdrawing group 吸电子基团
electrophile 亲电体
electrophilic aromatic substitution 芳香亲电取代
electrophoresis 电泳
eleostearic acid 桐油酸
eletrophilic 亲电的
elimination 消除，消去
empirical formula 实验式
emulsified 使乳化
emulsion 乳状液
enamine 烯胺
enantiomer 对映异构体
enantiomeric excess (ee) 对映体过量
enantiomerism 光学异构现象
enantioselective synthesis 对映选择性合成
endo position 内向位置
endothermic 吸热的
enediol 烯二醇
enolate ion 烯醇化离子
enol form 烯醇式
enol tautomer 烯醇互变异构体
enthalpy 焓
entropy 熵
enzymatic resolution 酶法拆分
enzyme 酶
ephedrine 麻黄碱(素)
epichlorohydrin 3-氯-1,2-环氧丙烷(表氯醇)
epimerization 差向异构
epimer 差向异构体
epinephrine 肾上腺素
epoxidation 环氧化反应
epoxide 环氧化物
epoxy resin 环氧树脂
equatorial bond 平伏键
equilibrium constant 平衡常数
erythro 赤型
erythrose 赤藓糖
essential oil 香精油
ester 酯
esterification 酯化
estradiol 雌二醇
ethanethiolate 乙硫醇盐
ethanolamine 乙醇胺
ether 醚
ethoxide 乙氧基
ethyl acetoacetate 乙酰乙酸乙酯
ethylammonium benzoate 苯甲酸乙铵
ethyl benzoate 苯甲酸乙酯
ethyl benzoylacetate 苯甲酰乙酸乙酯
ethyl carbamate 氨基甲酸乙酯
ethyl chloroformate 氯甲酸乙酯
ethyl diazoacetate 重氮乙酸乙酯
ethylene 乙烯
ethylene glycol 乙二醇
ethylene oxide 环氧乙烷
ethyl *N*-cyclohexyl carbamate *N*-环己基氨基甲酸乙酯
ethynyl estradiol 乙炔基雌二醇
excited state 激发态
exo position 外向位置
exothermic 放热的

F

farnesene 法呢烯
fatty acid 脂肪酸
fibrous protein 纤维状蛋白质
fingerprint region 指纹区
first order reaction 一级反应
fluocinolone acetonide 醋酸氟轻松
fluoro- 氟代
formaldehyde 甲醛
formalin 福尔马林
formate 甲酸盐
formic acid 甲酸
formyl chloride 甲酰氯
formyl 甲酰基
Fourier transform spectrometry 傅里叶变换光谱法

free energy	自由能
free radical	自由基
freon	氟利昂
fructofuranose	呋喃型果糖
fructofuranoside	呋喃型果糖苷
fructose	果糖
fullerene	富勒烯
fumaric acid	富马酸
fuming sulfuric acid	发烟硫酸
functional group	官能团
furan	呋喃
furanose	呋喃糖
fused ring	稠环

G

galactose	半乳糖
gas chromatograph（GC）	气相色谱
gauche conformation	邻位交叉构象
geminal dihalide	同碳二卤代物
geminal diol	偕二醇
gentiobiose	龙胆二糖
geometric isomer	几何异构体
geranial	香叶醛
geraniol	牛儿醇 香叶醇
geranium	老鹳草
geranyl acetate	乙酸香叶酯
globular protein	球状蛋白
globulin	球蛋白
glucitol	葡萄糖醇
gluconic acid	葡萄糖酸
glucopyranose	吡喃型葡萄糖
glucopyranoside	吡喃葡萄糖苷
glucose	葡萄糖
glucoside	葡萄糖苷
glutamic acid	谷氨酸
glutamine	谷氨酰胺
glycaric acid	糖二酸
glyceraldehyde	甘油醛
glyceride	甘油酯
glycerol	甘油
glycine	甘氨酸
glycogen	糖原
glycol	乙二醇
glycoprotein	糖蛋白
glycoside	苷
ground state	基态
guanidine	胍
guanine	鸟嘌呤
guanosine	鸟嘌呤核苷
guanylic acid	鸟苷酸
gulose	古洛糖
gyromagnetic ratio	回磁比

H

hydrate	水合物
half-chair conformation	半椅型构象
halide	卤化物
halide ion	卤离子
haloalkane	卤代烷烃
haloform	卤仿
halogenation	卤化
halohydrin	卤代醇
halonium ion	卤鎓离子
halo-substituent	卤代
hardener	固化剂
heat of combustion	燃烧热
α helix	α 螺旋
hemiacetal	半缩醛
hemlock	芹叶钩吻
hemoglobin	血红蛋白
heptalene	并庚间三烯
herring oil	鲱油脂
heteroatom	杂原子
heterocyclic compound	杂环化合物
heterogeneous catalysis	多相催化
heterolytic cleavage（ionic cleavage）	异裂
hexahelicene	六螺烯

high-density lipoprotein 高密度脂蛋白
high-resolution mass spectrometer 高分辨质谱仪
histamine 组胺
histidine 组氨酸
homogeneous phase 均相
homolog (homologous series) 同系物
homolytic cleavage (radical cleavage) 均裂
honeycomb 蜂房
hormone 激素
humulon 葎草酮
hybrid atomic orbital 杂原子轨道
hybridization 杂化
hydrate 水合物
hydrated lime 熟石灰
hydrazine 肼
hydrazone 腙
hydride 负氢
hydrin 醇（取代的醇词尾）
hydroboration 硼氢化作用
hydrobromic acid 氢溴酸
hydrocarbon 烃
hydrocracking 氢化裂解
hydrogenation 加氢，氢化（作用）
hydrogen bond 氢键
hydrogen-deuterium exchange 氢氘互换
hydrogenolysis 氢解作用
hydrogen peroxide (H_2O_2) 过氧化氢
hydrohalic acid 氢卤酸
hydroperoxide 氢过氧化物
hydrophilic 亲水的
hydrophobic 疏水的
hydroquinone (1,4-benzenediol) 氢醌（1,4－苯二酚）
hydroxide ion 氢氧根离子
hydroxylamine 羟胺
hydroxylation 羟基化
hydroxyl 羟基
hydroxymethylacetylene 羟甲基乙炔
hyperconjugation 超共轭
hypsochromic shift 蓝移

I

idose 艾杜糖
imidazole 咪唑
imine 亚胺
iminium salt 亚胺盐
index of hydrogen deficiency 缺氢指数
indole 吲哚
induced magnetic field 感应磁场
inductive effect 诱导效应
infrared spectrum 红外光谱
interferon 干扰素
intermediate 中间体
internal alkyne 内炔烃
invertase 转化酵素
invert sugar 转化糖
iodide 碘化物
iodo- 碘代
iodoform 碘仿
iodohydrin 碘代醇
iodomethylzinc iodide 碘甲基碘合锌
ionic bond 离子键
ionization 离子化，电离
isoamyl acetate 乙酸异戊酯（香蕉油）
isocyanate 异氰酸酯
isoelectric point 等电点
isoleucine 异亮氨酸
isoprene 橡胶基质
isotope effect 同位素效应
isovaleraldehyde 异戊醛
isovaleric acid 异戊酸
isovaleryl chloride 异戊酰氯
isoxazole 异噁唑

J

jasmone 茉莉酮

K

ketal	缩酮
keto-acid	酮－酸
keto-aldehyde	酮－醛
keto-enol tautomerism	酮－烯醇互变异构
keto ester	酮酯
keto form	酮式
ketohexose	己酮糖
ketone	酮
ketose	酮糖
ketotetrose	丁酮糖
kinetic control	动力学控制

L

lactam	内酰胺
lactone	内酯
lactose-intolerant	乳糖不耐症
lanosterol	羊毛甾醇
lauric acid	月桂酸
leaving group	离去基团
lecithin	卵磷脂
leucine	亮氨酸
levodopa(－)-dopa	左旋多巴
levorotatory	左旋的
levulose	果糖
lewisite	刘易士毒气
ligand	配体
limestone	石灰石
limonene	柠檬烯
linear combination of atomic orbital	原子轨道的线性组合
line-angle formula	键线－角构造式
linolenic acid	亚麻酸
linseed oil	亚麻子油
lipid	油脂
lipophilic	亲脂性的
lipoprotein	脂蛋白类
liquefied petroleum gas	液化石油气
lithium aluminum hydride	氢化锂铝
lithium dialkylcuprate	二烷基铜锂
lithium diisopropylamide	二异丙基氨基锂
lithium hydroxide	氢氧化锂
lone pair electrons	孤对电子
London dispersion force	London 色散力
lutidine	二甲基吡啶
lysine	赖氨酸
lyxose	来苏糖

M

magnesium monoperoxy-phthalate	单过氧化邻苯二酸镁
magnesium sulfate	硫酸镁
magnetic moment	磁矩
maleic acid	马来酸,顺丁烯二酸
malonic acid	丙二酸
malt	麦芽
maltose	麦芽糖
mannose	甘露糖
mass spectrometry	质谱
mechanism	机理
melting point	熔点
menthol	薄荷醇
mercapto	巯基
mercuric acetate	醋酸汞
mercuric sulfate	硫酸汞
mercurinium ion	汞正离子
meso compound	内消旋化合物
metaldehyde	四聚乙醛
metalloprotein	金属蛋白类
methane hydrate	甲烷水合物
methanesulfonic acid	甲磺酸
methanesulfonate ion	甲磺酸离子
methine	亚甲基

methionine	蛋氨酸;甲硫氨酸
methoxide ion	甲氧基离子
methoxybenzene	甲氧基苯（茴香醚）
methylammonium chloride	甲基氯化铵
methyl benzoate	苯甲酸甲酯
methyl α-cyanoacrylate	α-氰基丙烯酸甲酯
methylene chloride（dichloromethane）	二氯甲烷
methylene	亚甲基
methylene iodide	二碘甲烷
methyl formate	甲酸甲酯
methyl	甲基
methylmagnesium iodide	甲基碘合镁
methyl orange	甲基橙
N-methylpyridinium iodide	*N*-甲基吡啶碘盐
methyltriphenylphosphonium salt	甲基三苯基季鏻盐
micelle	胶囊
molecular formula	分子式
molecular orbital	分子轨道
molecular sieve	分子筛
molozonide	分子臭氧化物
monomer	单体
monosaccharide	单糖
monoterpene	单萜
morphine	吗啡
multiplet	多重峰
muscalure	家蝇引诱剂
muscone	麝香酮
musky aroma	麝香
mutarotation	变旋光现象
mylar polyester	聚酯薄膜
myrcene	月桂烯
myristic acid	肉豆蔻酸

N

nanotube	纳米管
naphthalene	萘
naphthol	萘酚
naphthyl	萘基
neopentane	新戊烷
neopentyl alcohol	新戊醇
Newman projection	纽曼投影式
nickel-aluminum alloy	镍-铝合金
nickel boride	硼化镍
nicotinamide	烟酰胺
nicotine	烟碱
nicotinic acid	烟酸
nicotinonitrile	烟腈
ninhydrin	水合茚三酮
nitric acid	硝酸
nitrile	腈
nitro	硝基
nitroso	亚硝基
nitrosonium ion	亚硝基鎓离子
nitrous acid	亚硝酸
nodal plane	节面
node（nodal point）	节点
nomenclature	命名法
nonbonding electron	非键(合)电子
nonpolar covalent bond	非极性共价键
norbornane (bicycle[2,2,1]heptane)	降莰烷（环[2,2,1]庚烷）
norbornene	降冰片烯
norcarane	降蒈烷
nuclear magnetic resonance spectrum	核磁共振谱
nucleophile	亲核试剂
nucleophilic addition	亲核加成
nucleophilic aromatic substitution	芳香亲核取代
nucleophilicity	亲核性
nucleophilic substitution	亲核取代
nucleoprotein	核蛋白类
nucleotide	核苷
nylon	尼龙

O

octane number	辛烷值
octet rule	八隅体规则

off-resonance decoupling	偏共振去偶
oil of bay	月桂油
oil of celery	芹菜油
olefin	烯烃
oleic acid	油酸
oleoyl chloride	油酰氯
oligopeptide	寡肽
oligosaccharide	低聚糖，寡糖
olive oil	橄榄油
optical activity	光学活性
optical isomer	光学异构体
organolithium reagent	有机锂试剂
organomagnesium halide (Grignard reagent)	有机镁卤化物（格氏试剂）
organometallic compound	金属有机化合物
organometallic reagent	金属有机试剂
osazone	脎
osmic acid	锇酸
osmium tetroxide	四氧化锇
oxalic acid	草酸
oxalyl chloride	草酰氯
oxide	氧化物
oxime	肟
oxirane	环氧乙烷
oxymercuration-demercuration	氧化加汞－脱汞作用
ozone (O_3)	臭氧
ozonide	臭氧化物
ozonolysis	臭氧分解

P

palmitic acid	软脂酸
paraformaldehyde	低聚甲醛
paraldehyde	三聚乙醛
pauli exclusion principle	泡利不相容原理
penicillin G	青霉素 G
pentalene	并环戊二烯
peptide	肽
peracid	过酸
periodic acid	高碘酸
peroxide	过氧化物
peroxyacetic acid	过氧乙酸
peroxybenzoic acid	过氧苯甲酸
phase-transfer catalysts	相转移催化剂
phenacetin	非那西汀
phenanthrene	菲
phenol	苯酚
phenol-formaldehyde resins	酚醛树脂
phenoxide	酚盐
phentermine	苯丁胺
phenylalanine benzyl ester	苯丙氨酸苄酯
phenyl	苯基
phenylhydrazine	苯肼
phenylhydrazone	苯腙
phenyllithium	苯基锂
phenylmagnesium bromide	苯基溴化镁
phenyl-2-propanone oxime	苯基－2－丙酮肟
phenylthiohydantoin	苯乙内酰硫脲
phenylthiourea	苯硫脲
phosgene	光气
phosphate ion	磷酸盐离子
phosphatidic acid	磷脂酸
phosphatidyl choline	磷脂酰胆碱
phosphatidyl ethanolamine	磷脂酰乙醇胺
phosphine	磷化氢，膦
phosphoglyceride	磷酸甘油酯
phospholipid	磷脂
phosphonium salt	鏻盐
phosphoric acid	磷酸
phosphorus halide	磷的卤化物
phosphorus oxychloride	三氯氧磷
phosphorus pentachloride	五氯化磷
phosphorus trichloride	三氯化磷
phosphorus ylide	磷叶立德
photolysis	光解作用
photon	光子
photosynthesis	光合作用
phthalic acid	邻苯二甲酸
phthalimide	邻苯二甲酰亚胺
phthalimide hydrazide	邻苯二甲酰肼
phthalimidomalonic ester	邻苯二甲酰亚氨基丙二酸酯
pinacol	频哪醇

pinacolone	频哪酮
pinene	松萜,蒎烯
piperazine	哌嗪
piperidine	哌啶
plane of polarized light	偏振光平面
polar aprotic solvent	极性非质子型溶剂
polar covalent bond	极性共价键
polarimeter	偏振器
polarimetry	偏振测定法
polarity	极性
polarizability	极化性
poly	聚
polycarbonate	聚碳酸酯
polyester	聚酯
polyethylene	聚乙烯
polymer	聚合体,聚合物
polymerization	聚合
polymerize	使聚合
polymer monomer	聚合物单体
polynuclear aromatic hydrocarbon	多核芳香烃化合物
polypeptide	多肽
polysaccharide	多糖
polyurethane	聚氨基甲酸乙酯
potassium *t*-butoxide	叔丁醇钾
potassium hydroxide	氢氧化钾
potassium permanganate	高锰酸钾
potential energy	势能
primary	伯
prion protein	朊蛋白
proline	脯氨酸
proline benzyl ester	脯氨酸苄酯
propadiene	丙二烯
propagation step	链增长阶段
propanal cyanohydrin	丙醛羟腈
propargyl alcohol	丙炔醇
propionaldehyde	丙醛
propionic acid	丙酸
propionitrile	丙腈
propiophenone	苯丙酮
propyl	丙基
propylammonium chloride	丙基氯化铵
propylene glycol	丙二醇
propylene oxide	环氧丙烷
prostaglandin	前列腺素
protecting group	保护基
protein	蛋白质
protic solvent	质子型溶剂
protonated	质子化的
protonation	质子化作用
proton spin decoupling	质子自旋去偶
purine	嘌呤
putrescine	腐胺
pyramidal	锥体的
pyran	吡喃
pyranose	吡喃糖
pyrene	芘
pyrethrin	除虫菊酯
pyridine	吡啶
pyridine *N*-oxide	*N*-吡啶氧化物
pyridinium acetate	吡啶乙酸盐
pyridinium chlorochromate (PCC)	氯铬酸吡啶鎓(沙瑞特试剂)
pyridinium ion	吡啶鎓离子
pyridoxine	吡哆素
pyrimidine	嘧啶
pyrone	吡喃酮
pyrrole	吡咯
pyrrolidine	四氢吡咯
pyrylium ion	吡喃鎓离子

Q

quantum yield	量子产率
quartet	四重峰
quaternary ammonium hydroxide	季铵碱
quaternary ammonium salt	季铵盐
quinine	奎宁
quinoline	喹啉
quinone (1,4-benzoquinone)	醌(1,4-苯醌)

R

racemate	外消旋体	resonance effect	共振效应
racemization	外消旋化	resonance energy	共振能
rate-determining step	控速步骤	resonance hybrid	共振杂化体
rate-limiting step	限速步骤	retinal (vitamin A)	视黄醇（维生素 A）
rayon	人造纤维	retrosynthetic analysis	逆合成分析
reducing sugar	还原糖	ribofuranose	呋喃核糖
reductive amination	还原胺化	ribonucleic acid (RNA)	核糖核酸
regioselective	区域选择性	ribonucleoside	核糖核苷
resolution of enantiomer	对映体拆分	ribose	核糖
resolving agent	拆分试剂	ring strain	环张力
resonance-delocalized	共振-离域的	rotational barrier	旋转势垒

S

saccharic acid	糖二酸	sodium ethoxide	乙氧基钠
salicylic acid	水杨酸（邻羟基苯甲酸）	sodium hydride	氢化钠
saponification	皂化	sodium hydroxide	氢氧化钠
sawhorse structure	锯木架结构	sodium hypochlorite	次氯酸钠
secondary	仲	sodium nitrite	亚硝酸钠
second order reaction	二级反应	sodium phenoxide	苯酚钠
selinene	蛇床烯,芹子烯	sodium stearate	硬脂酸钠
semicarbazide	氨基脲	solute	溶质
semicarbazone	缩氨基脲,半卡巴腙	solvation	溶剂化作用
serine	丝氨酸	solvent	溶剂
sesquiterpene	倍半萜	solvolysis	溶剂分解(作用)
shielded	被屏蔽	sorbitol	甘露醇
silver nitrate	硝酸银	spearmint oil	留兰香油
single bond	单键	specific rotation	比旋光率
skeletal structure	骨架结构	spermaceti	鲸油
sodium alkoxide	醇钠	spin-spin splitting	自旋-自旋裂分
sodium amide	氨基钠	spirocyclic	螺环的
sodium azide	叠氮酸钠	squalene	角鲨烯
sodium borohydride	硼氢化钠	staggered conformation	交叉式构象
sodium butyne	丁炔钠	sterculic acid	亚甲基油酸
sodium carbonate	碳酸钠	stereocenter (stereogenic atom)	立体中心
sodium chloride	氯化钠	stereoisomer	立体异构体
sodium cyanide	氰化钠	stereospecific	立体专一性的
sodium acetylide	乙炔钠	steric hindrance	位阻(现象)
sodium dichromate	重铬酸钠	straight-chain alkane	直链烷烃
sodium ethanethiolate	乙硫醇钠	stearic acid	硬脂酸
		stereochemistry	立体化学

English	中文
stereoisomer	立体异构体
steric effect	空间效应
steric hindrance	空间位阻
steroid	甾族化合物
styrene (vinylbenzene)	苯乙烯
substituent	取代基
substituted	取代的
substitution	取代作用
substrate	底物
succinimide	琥珀酰亚胺
sucrose	蔗糖
sulfa drug	磺胺类药物
sulfanilamide	磺胺,对氨基苯磺酰胺
sulfate ion	硫酸盐离子
sulfide (thioether)	硫醚 硫化物
sulfonamide	磺酰胺
sulfonate ion	磺酸盐离子
sulfone	砜
sulfonic acid	磺酸
sulfonium salt	锍盐
sulfonyl chloride	磺酰氯
sulfoxide	亚砜
sulfuric acid	硫酸
superimposable	可重叠的
syn addition	顺式加成
syn-coplanar	顺式共平面

T

English	中文
talose	塔罗糖
tartaric acid	酒石酸
tartrate	酒石酸盐(酯)
tautomer	互变异构体
tautomerize	互变异构
temporary dipole moment	瞬间偶极矩
terminal alkyne	端炔
termination step	链终止阶段
terpene	萜
terpenoid	萜类化合物
tert-butyl	叔丁基
tert-butyl hydroperoxide	叔丁基氢过氧化物
tertiary	叔
tertiary alcohol	叔醇
testosterone	睾丸酮
tetrachloromethane(carbon tetrachloride)	四氯化碳
tetraene	四烯烃
tetrafluoroethylene	四氟乙烯
tetrahedral	四面体的
tetrahydrofuran (THF)	四氢呋喃
tetrahydrofurfuryl alcohol	四氢糠醇
tetrahydropyran	四氢吡喃
thermodynamics	热力学
thermodynamic control	热力学控制
thiazole	噻唑
thiazolinone	噻唑啉酮
thioacetal	缩硫醛
thioester	硫酯
thioether(sulfide)	硫醚
thioketal	缩硫酮
thiol (mercaptan)	硫醇
thiolate	硫醇盐
thionyl chloride	二氯亚砜
thiophene	噻吩
threo	苏式
threose	苏糖
thymine	胸腺嘧啶
thyroid hormone	甲状腺激素
thyroxine	甲状腺素,甲状腺氨酸
titanium(Ⅳ) isopropoxide	四异丙氧基钛
toluamide	甲基苯甲酰胺
toluene	甲苯
toluene diisocyanate	甲苯二异氰酸酯
p-toluenesulfonic acid	对甲苯磺酸
p-toluenesulfonyl chloride	对甲苯磺酰氯
toluidine	甲苯胺
tosylate	甲苯磺酸盐
tosylate ester	甲苯磺酸酯
tosylate ion	甲苯磺酸盐离子
tosylation	甲苯磺酰化
tosyl chloride	甲苯磺酰氯
toxin	毒素
trans	反

transesterification	酯交换
transition state	过渡态
trialkyl borate ester	三烷基硼酸酯
tricosene	二十三烯
triene	三烯烃
triethylamine	三乙胺
triethylammonium hydrogen sulfate	硫酸氢化三乙基铵
trifluoroacetate	三氟乙酸
triglyceride (triacylglycerol)	甘油三酸酯
trimethylamine	三甲胺
trimethylanilinium iodide	碘化三甲基苯胺
trimethylsulfonium iodide	碘化三甲基锍
triolein	三油酸甘油酯
trioxane	三氧杂环己烷,三嗯烷
triphenylphosphine (PPh_3)	三苯基膦
triphenylphosphine oxide	三苯氧膦
triple bond	三键
triplet	三重峰
tristearin	三硬脂酸甘油酯
triethanolamine	三乙醇胺
tropylium ion	卓鎓离子
tryptophan	色氨酸
turpentine	松脂
twist boat conformation	扭曲船型构象
tyrosine	酪氨酸
tyrosine phenylthiohydantoin	酪氨酸苯乙内酰硫脲

U

ultraviolet (UV) spectroscopy	紫外光谱
umbelliferone	7-羟基香豆素
uracil	尿嘧啶
urea	尿素
urea-formaldehyde glue	脲醛树脂胶
uridine	尿嘧啶核苷
uridine monophosphate (uridylic acid)	尿苷一磷酸(尿苷酸)

V

valence	化合价
valence electron	价电子
valence shell	价电子层
valine	缬氨酸
vanilla	香草
vanillin	香兰素
vasodilator	血管扩张药
vegetable shortening	植物油制的起酥油
vicinal dihalide	邻碳二卤代物
vicinal diol	邻二醇
vinyl	乙烯基
vinyl halide	卤代乙烯
viscosity	黏度
vitalism	活机论,生机说
volatility	挥发性

W

wave function	波函数
wavenumber	波数

X

xanthate	黄原酸盐(或酯)
X-ray crystallography	X 射线晶体学
xylene	二甲苯
xylose	木糖

Z

zinc chloride	氯化锌
zingiberene	姜烯

Typical Values of Proton NMR Chemical Shifts

Type of Proton		Approximate δ
alkane (—CH_3)	methyl	0.9
alkane (—CH_2—)	methylene	1.3
alkane (—CH(—)—)	methine	1.4
—C(=O)—CH_3	methyl ketone	2.1
—C≡C—H	acetylenic	2.5
R—CH_2—X	(X = halogen, —O—)	3–4
>C=C< with H	vinyl	5–6
>C=C< with CH_3	allylic	1.7
Ph—H	aromatic	7.2
Ph—CH_3	benzylic	2.3
R—CHO	aldehyde	9–10
R—COOH	acid	10–12
R—OH	alcohol	variable, about 2–5
Ar—OH	phenol	variable, about 4–7
R—NH_2	amine	variable, about 1.5–4

These values are approximate, because all chemical shifts are affected by neighboring substituents. The numbers given here assume that alkyl groups are the only other substituents present.

Typical Values of IR Stretching Frequencies

Frequency	Functional Group		Comments
3 300 cm^{-1}	alcohol	O—H	Always broad
	amine, amide	N—H	May be broad, sharp, or broad with spikes
	alkyne	≡C—H	Always sharp, usually strong
3 000 cm^{-1}	alkane	—C(—)(—)—H	Just below 3 000 cm^{-1}
	alkene	=C(—H)<	Just above 3 000 cm^{-1}
	acid	O—H	Very broad 2 500–3 500 cm^{-1}
2 200 cm^{-1}	alkyne	—C≡C—	Just below 2 200 cm^{-1}
	nitrile	—C≡N	Just above 2 200 cm^{-1}
1 710 cm^{-1} (very strong)	carbonyl (very strong)	>C=O	Ketones, aldehydes, acids Esters higher, about 1 735 cm^{-1} Conjugation lowers frequency Amides lower, about 1 650 cm^{-1}

Continue

Frequency	Functional Group		Comments
$1\,660\ cm^{-1}$	alkene	$>C=C<$	Conjugation lowers frequency Aromatic $C=C$ about $1600\ cm^{-1}$
	imine	$>C=N-$	Stronger than $C=C$
	amide	$>C=O$	Stronger than $C=C$ (see above)

Ethers, esters, and alcohols also show C—O stretching between $1\,000$ and $1\,200\ cm^{-1}$.

Summary of Functional Group Nomenclature

Functional Group	Name as Main Group	Name as Substituent
Main groups in order of decreasing priority		
carboxylic acids	- oic acid	carboxy
esters	- oate	alkoxycarbonyl
amides	- amide	amido
nitriles	- nitrile	cyano
aldehydes	- al	formyl
ketones	- one	oxo
alcohols	- ol	hydroxy
amines	- amine	amino
alkenes	- ene	alkenyl
alkynes	- yne	alkynyl
alkanes	- ane	alkyl
ethers		alkoxy
halides		halo

Periodic Table of the Elements

6	— Atomic number
C	— Element symbol
12.01	— Atomic weight*
Carbon	— Element name

PERIOD	1A	2A	3B	4B	5B	6B	7B	8B	8B	8B	1B	2B	3A	4A	5A	6A	7A	Noble gases 8A
1	1 **H** 1.008 Hydrogen																	2 **He** 4.003 Helium
2	3 **Li** 6.941 Lithium	4 **Be** 9.012 Beryllium											5 **B** 10.81 Boron	6 **C** 12.01 Carbon	7 **N** 14.01 Nitrogen	8 **O** 16 Oxygen	9 **F** 19.00 Fluorine	10 **Ne** 20.18 Neon
3	11 **Na** 22.99 Sodium	12 **Mg** 24.31 Magnesium											13 **Al** 26.98 Aluminum	14 **Si** 28.09 Silicon	15 **P** 30.97 Phosphorus	16 **S** 32.07 Sulfur	17 **Cl** 35.45 Chlorine	18 **Ar** 39.95 Argon
4	19 **K** 39.10 Potassium	20 **Ca** 40.08 Calcium	21 **Sc** 44.96 Scandium	22 **Ti** 47.867 Titanium	23 **V** 50.94 Vanadium	24 **Cr** 52.00 Chromium	25 **Mn** 54.94 Manganese	26 **Fe** 55.85 Iron	27 **Co** 58.93 Cobalt	28 **Ni** 58.70 Nickel	29 **Cu** 63.546 Copper	30 **Zn** 65.39 Zinc	31 **Ga** 69.72 Gallium	32 **Ge** 72.64 Germanium	33 **As** 74.92 Arsenic	34 **Se** 78.96 Selenium	35 **Br** 79.90 Bromine	36 **Kr** 83.80 Krypton
5	37 **Rb** 85.47 Rubidium	38 **Sr** 87.62 Strontium	39 **Y** 88.91 Yttrium	40 **Zr** 91.22 Zirconium	41 **Nb** 92.90 Niobium	42 **Mo** 95.94 Molybdenum	43 **Tc** (98) Technetium	44 **Ru** 101.07 Ruthenium	45 **Rh** 102.9 Rhodium	46 **Pd** 106.4 Palladium	47 **Ag** 107.9 Silver	48 **Cd** 112.4 Cadmium	49 **In** 114.8 Indium	50 **Sn** 118.7 Tin	51 **Sb** 121.8 Antimony	52 **Te** 127.6 Tellurium	53 **I** 126.9 Iodine	54 **Xe** 131.3 Xenon
6	55 **Cs** 132.9 Cesium	56 **Ba** 137.327 Barium	71 **Lu** 175.0 Lutetium	72 **Hf** 178.5 Hafnium	73 **Ta** 180.9479 Tantalum	74 **W** 183.84 Tungsten	75 **Re** 186.2 Rhenium	76 **Os** 190.23 Osmium	77 **Ir** 192.2 Iridium	78 **Pt** 195.1 Platinum	79 **Au** 197.0 Gold	80 **Hg** 200.6 Mercury	81 **Tl** 204.4 Thallium	82 **Pb** 207.2 Lead	83 **Bi** 209.0 Bismuth	84 **Po** (209) Polonium	85 **At** (210) Astatine	86 **Rn** (222) Radon
7	87 **Fr** (223) Francium	88 **Ra** (226) Radium	103 **Lr** (257) Lawrencium	104 **Rf** (261) Rutherfordium	105 **Db** (262) Dubnium	106 **Sg** (263) Seaborgium	107 **Bh** (262) Bohrium	108 **Hs** (265) Hassium	109 **Mt** (266) Meitnerium	110 (269)	111 (272)	112 (277)		114 (285)		116 (289)		

* Lanthanide series:	57 **·La** 138.9 Lanthanum	58 **Ce** 140.1 Cerium	59 **Pr** 140.9 Praseodymium	60 **Nd** 144.2 Neodymium	61 **Pm** (145) Promethium	62 **Sm** 150.4 Samarium	63 **Eu** 152.0 Europium	64 **Gd** 157.3 Gadolinium	65 **Tb** 158.9 Terbium	66 **Dy** 162.5 Dyprosium	67 **Ho** 164.9 Holmium	68 **Er** 167.3 Erbium	69 **Tm** 168.9 Thulium	70 **Yb** 173.0 Ytterbium
†Actinide series:	89 **†Ac** (227) Actinium	90 **Th** 232.0 Thorium	91 **Pa** (231) Protactinium	92 **U** 238.0 Uranium	93 **Np** (237) Neptunium	94 **Pu** (244) Plutonium	95 **Am** (243) Americium	96 **Cm** (247) Curium	97 **Bk** (247) Berkelium	98 **Cf** (251) Californium	99 **Es** (252) Einsteinium	100 **Fm** (257) Fermium	101 **Md** (258.10) Mendelevium	102 **No** (259) Nobellium

* Numbers in parentheses are mass numbers of the most stable or best-known isotope of radioactive elements.

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